Thérapie Phagique,
Ou en sommes nous ?

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Centre de Référence des IOA complexes de Lyon (CRIOAc Lyon)

@FerryLyon

Centre de Référence des Infections Ostéo-Articulaires complexes
CRIOAc

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CRIOAc

STAPHYLOCOQUES
Centre National de Référence

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Microbiologist

UCBL Lyon

IAI CBPN

Inserm

CRB
Centre de Ressources Biologiques

ciri
Centre International de Recherche en Infectiologie

HCL
HOSPICES CIVILS DE LYON

Réseau des CRIOAc

CRIOAc
LYON

CENTRES DE RÉFÉRENCE POUR LES INFECTIONS OSTÉO-ARTICULAIRES COMPLEXES DU GRAND OUEST
CRIOGO

CENTRES DE RÉFÉRENCE DES INFECTIONS OSTÉO-ARTICULAIRES COMPLEXES
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ILE DE FRANCE

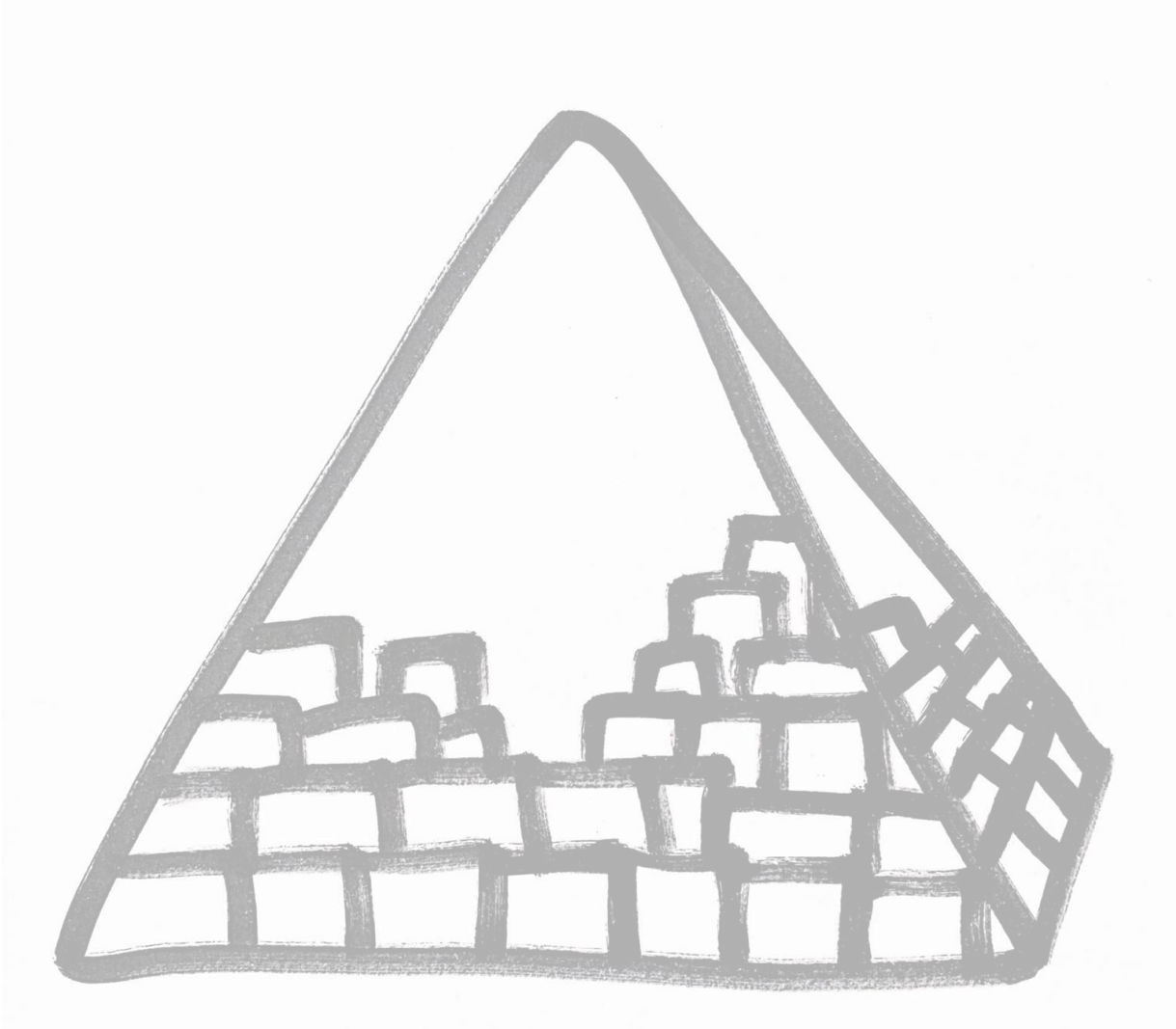
CRIOAC
Grand Est

g4CRIOAC
Centre de Référence des Infections Ostéo Articulaires Complexes

Hôpitaux Universitaires de Marseille | ap hm

Crioac
GSO

Personalized medicine for BJI



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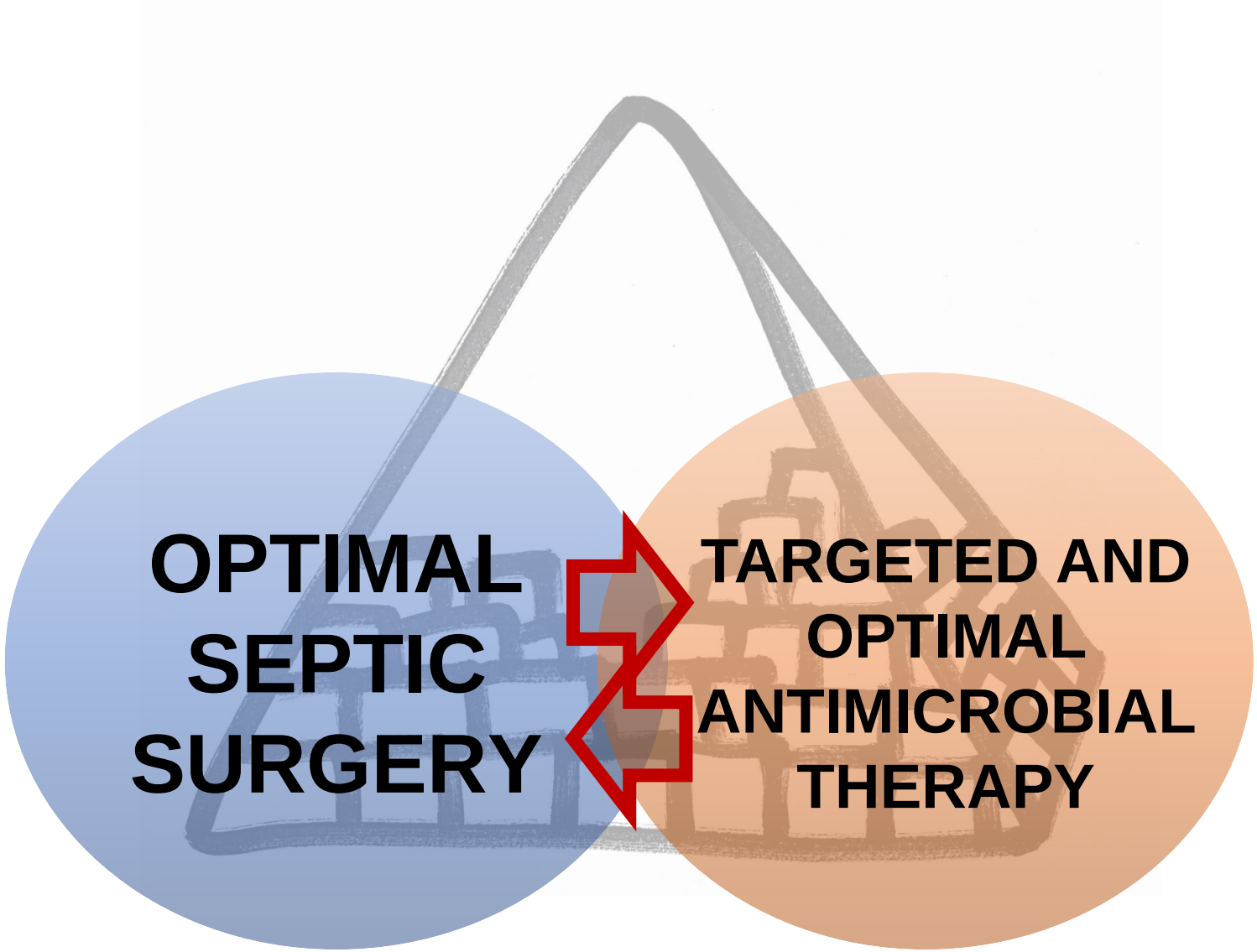

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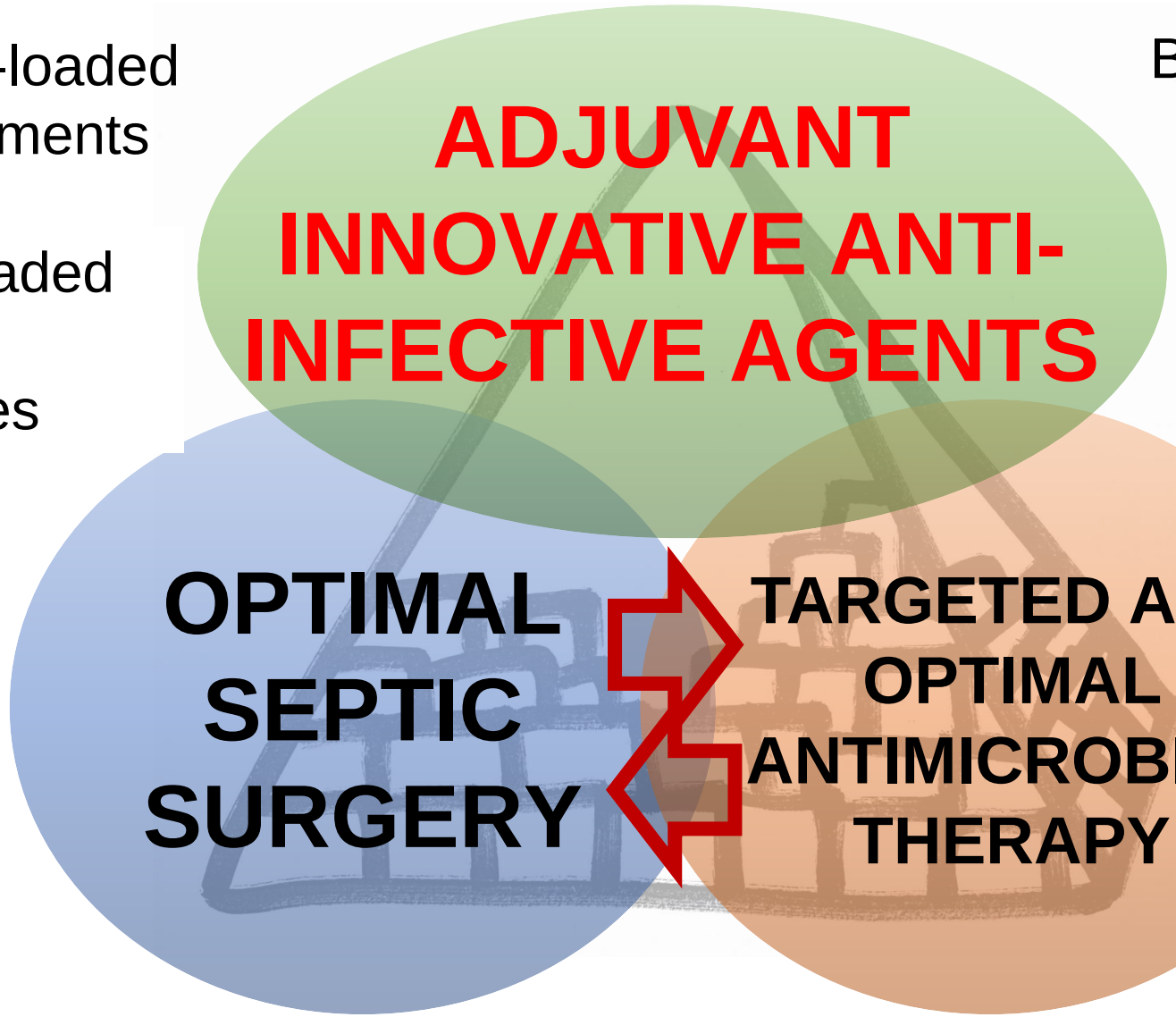


Antibiotics-loaded PMMA cements

Antibiotic-loaded bone substitutes

Bacteriophages

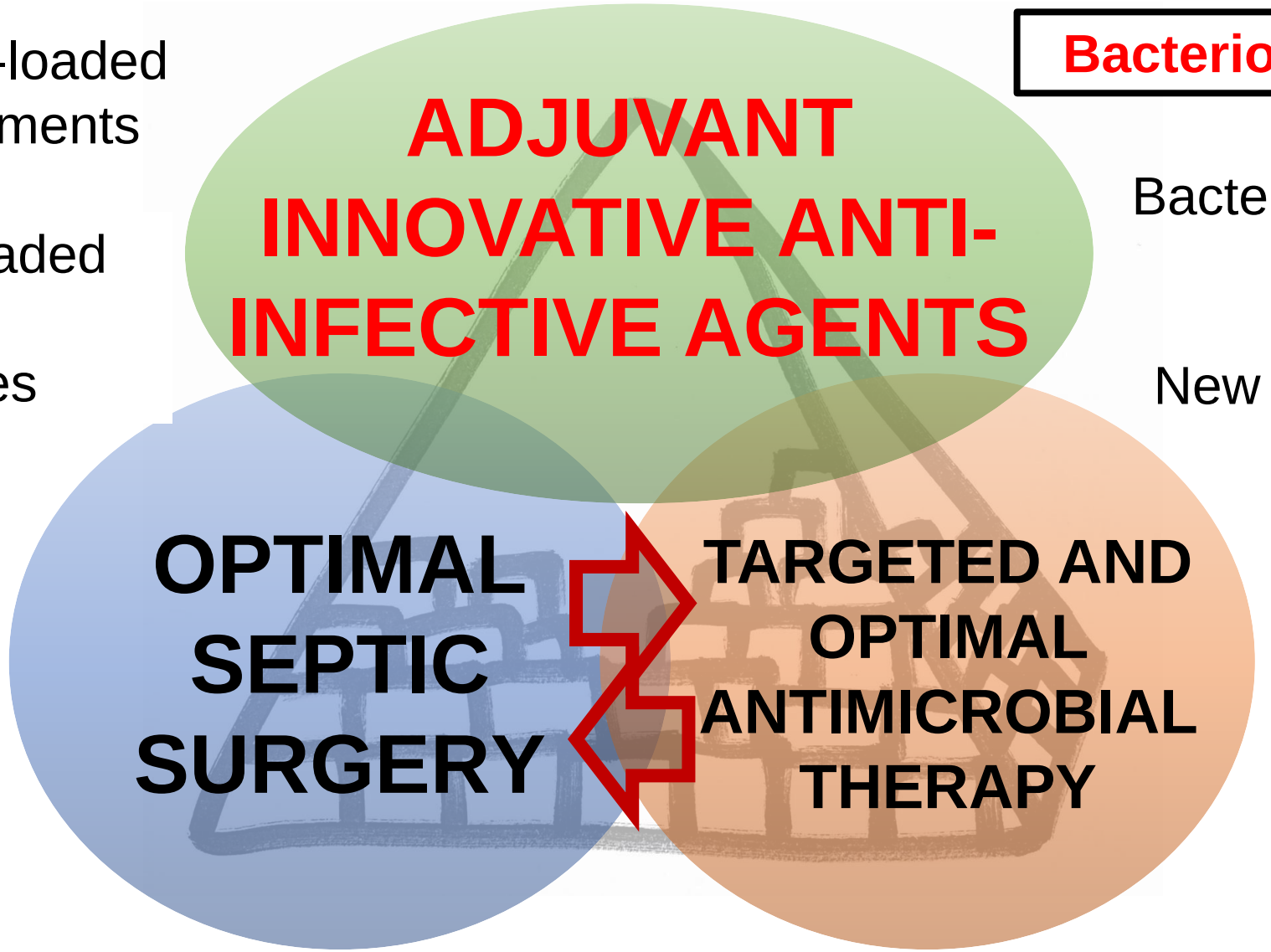
Bacteriophage-derived lysins

New antibiotics targeting the biofilm

New antibiotics usable for SAT

Subcutaneous personalized SAT

Personalized medicine for BJI



AntibioticS-loaded PMMA cements

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New antibiotics targeting the biofilm

New antibiotics usable for SAT

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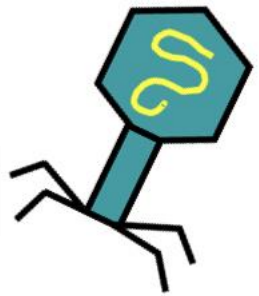
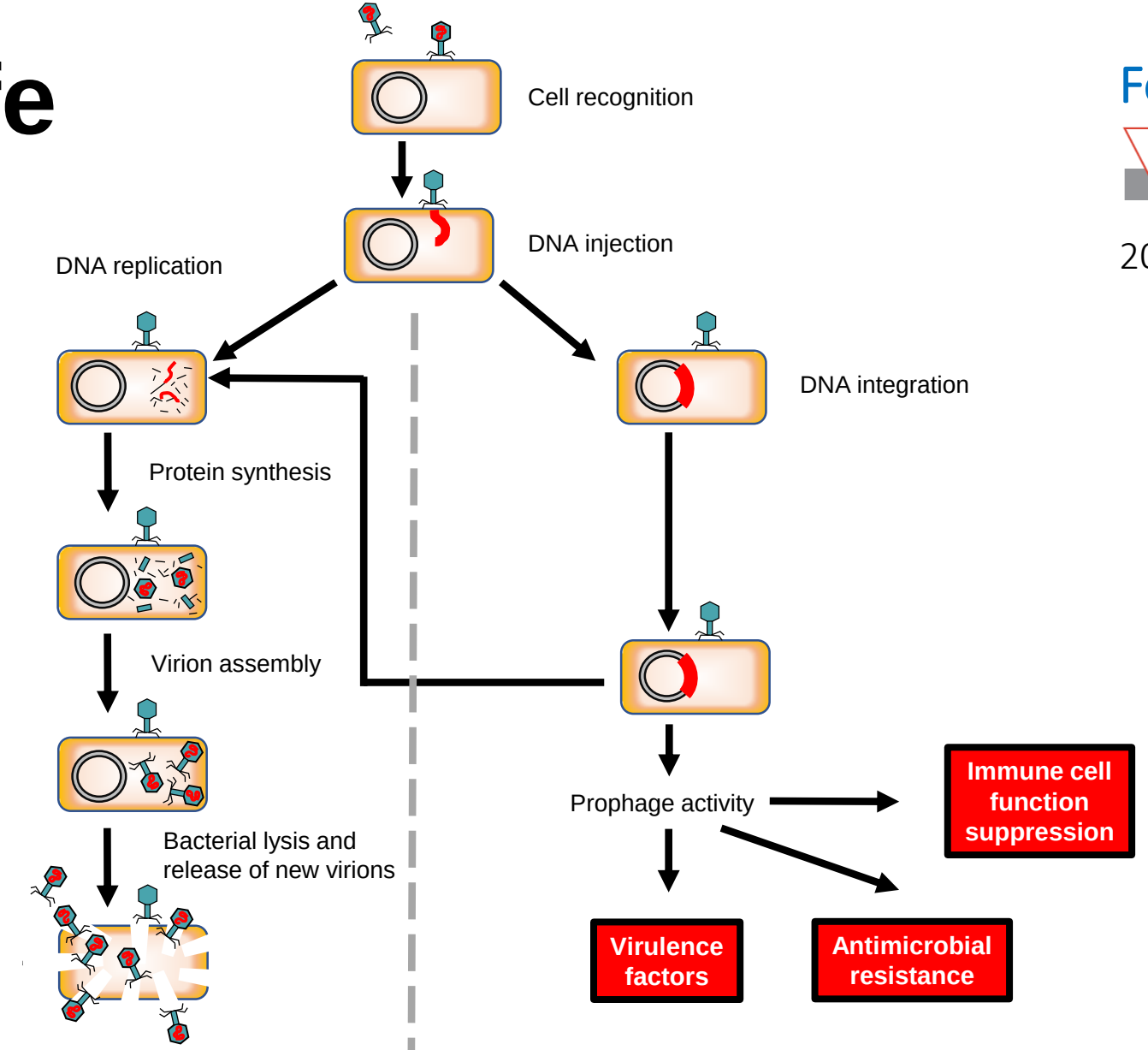
What is a « bacteriophage » ?



- Suffix –phage, *phagos* φαγεῖν (*phagein*), "to eat", “to devour"
- **Viruses that infect ONLY bacteria**
- Classification (*myoviridae, podoviridae, etc…)*
- **A phage is specific to A type of bacteria**
- **Largely abundant in the biosphere: 10^{31} bacteriophages on the planet, more than every other organism**
- Especially in marine environment, sea, lake, backwater, soil, animal and human stools, etc.

The phage life

Ferry T. et al.
Virologie
2020;24(1):49-56



Lytic cycle

Self-maintained bacterial lysis

Lysogenic cycle

Bacterial genetic remodeling

The phage life

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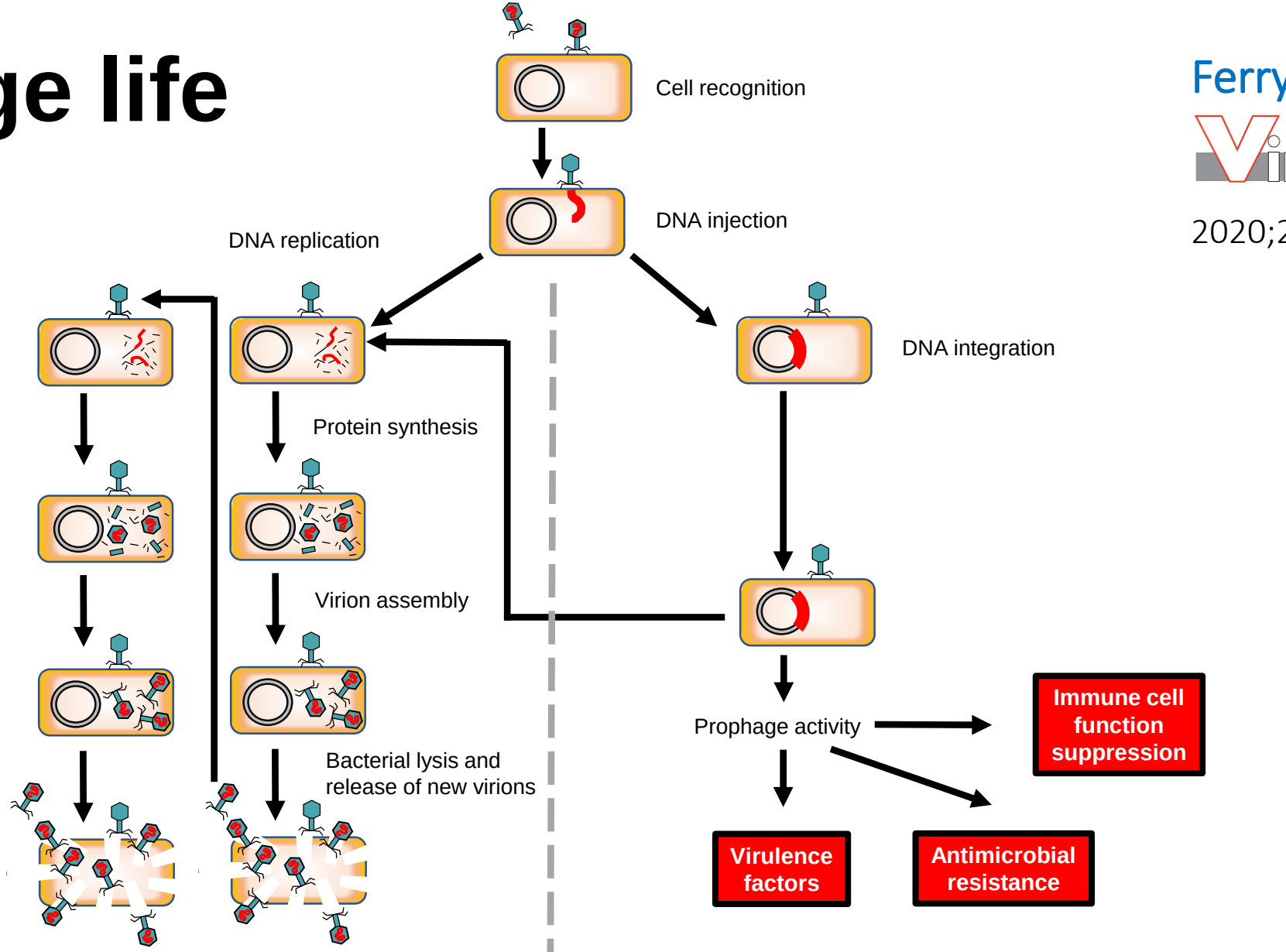

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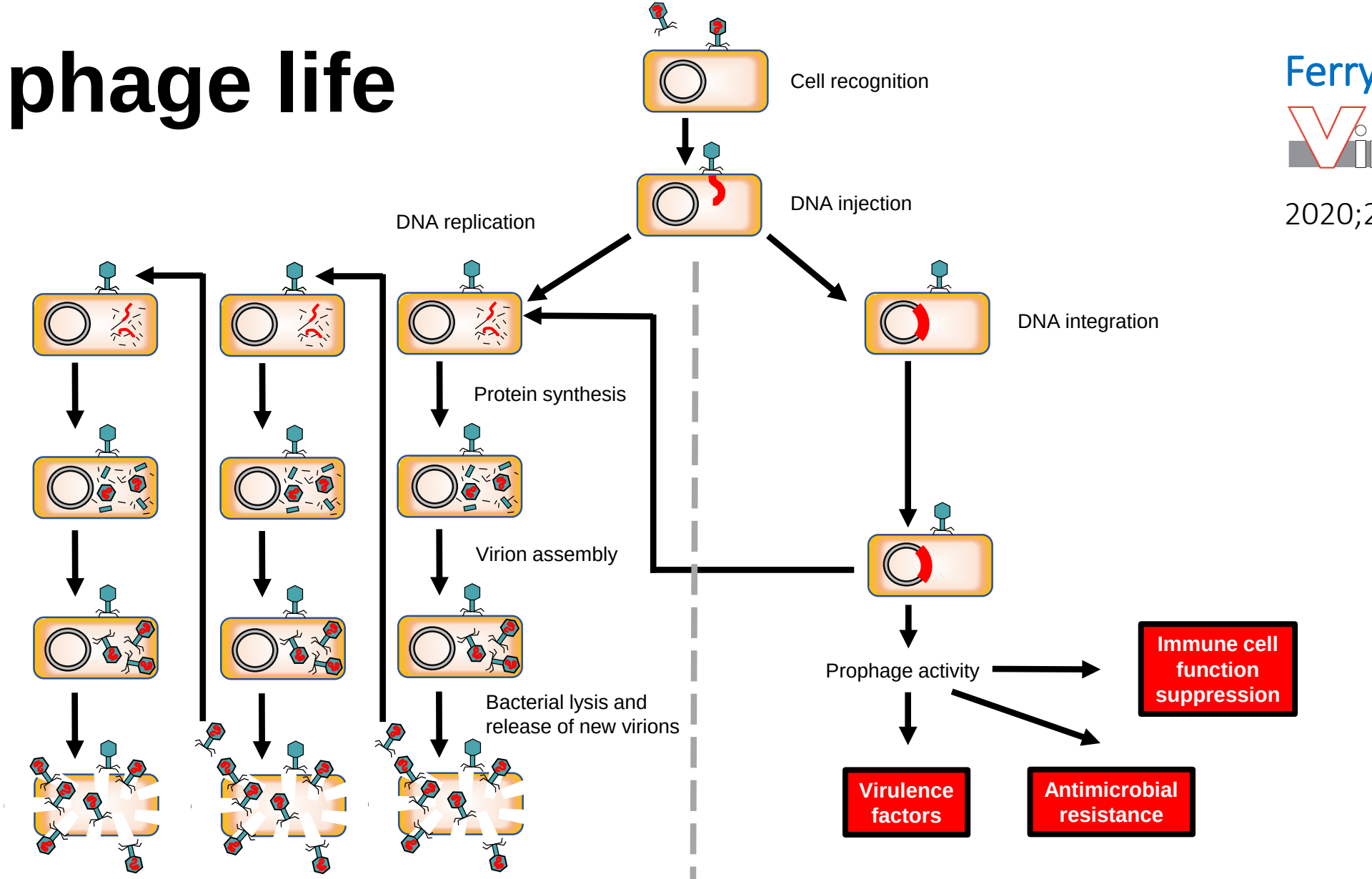


Lytic cycle

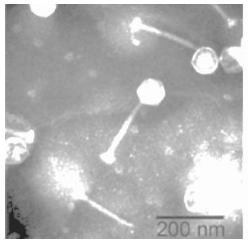
Self-maintained bacterial lysis

Lysogenic cycle

Bacterial genetic remodeling

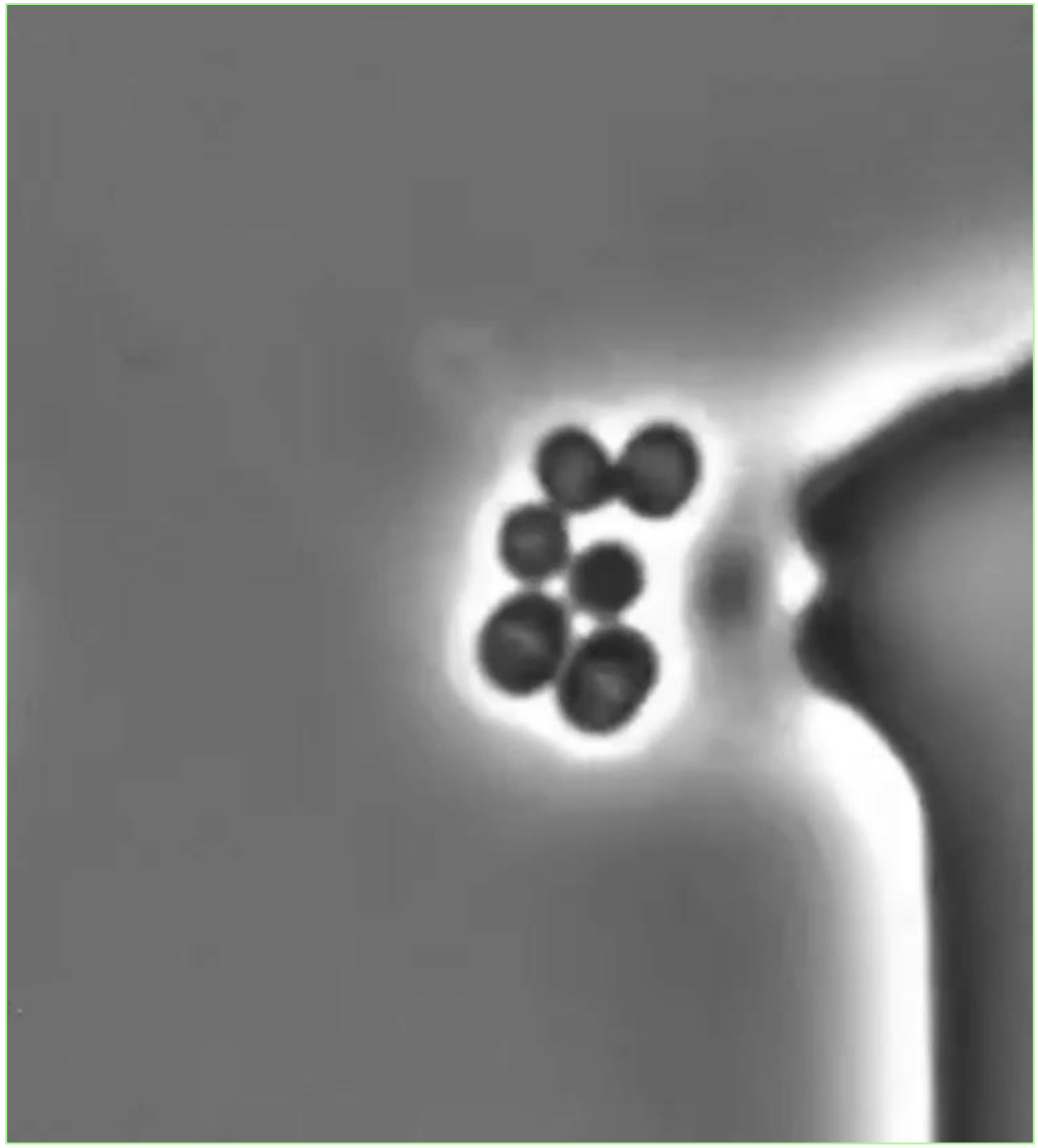
Only lytic phages have to be used

***S. aureus* being lysed by the Sa2 phage**

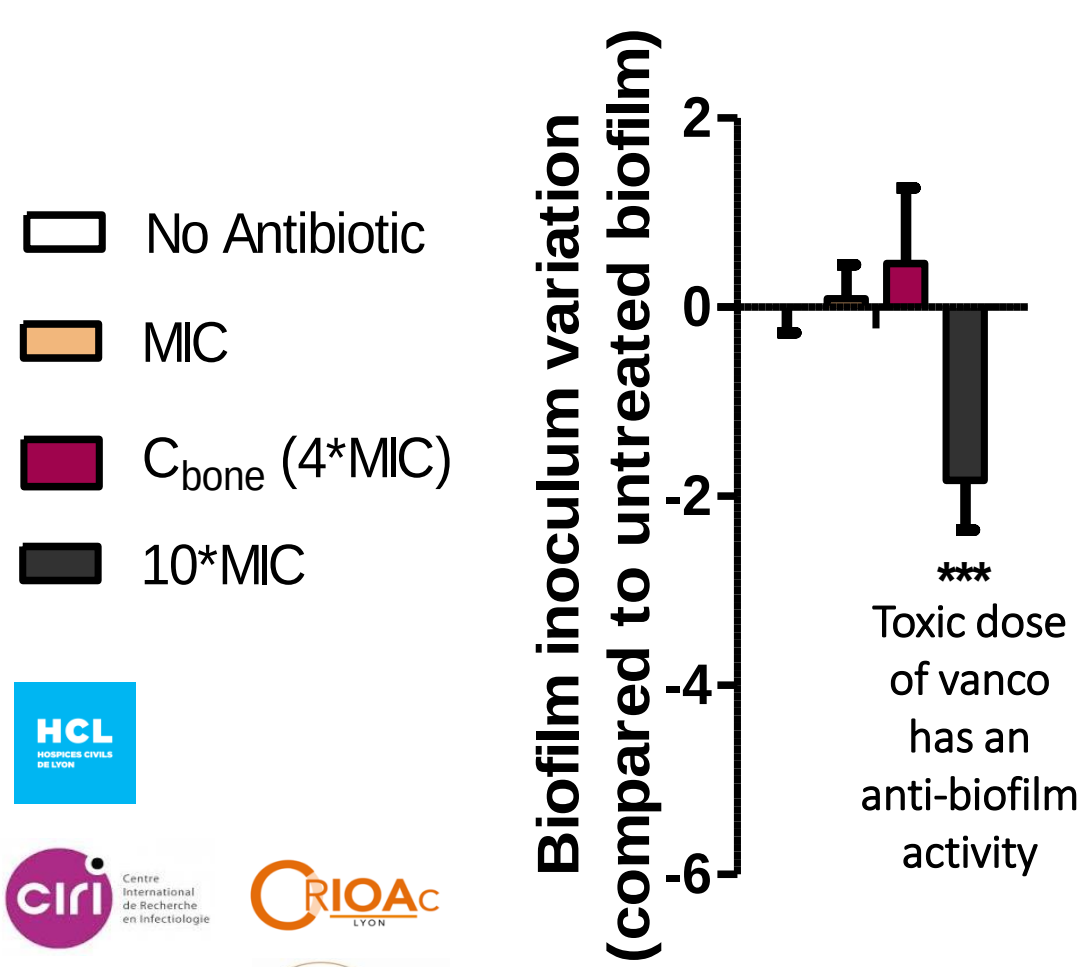


Bacterial DNA appeared in green

Courtesy Pascal Maguin
Luciano Marraffini Lab
THE ROCKEFELLER UNIVERSITY



Phages have antibiofilm activity



C. Kolenda et al. Antimicrob Agents Chemother 2019

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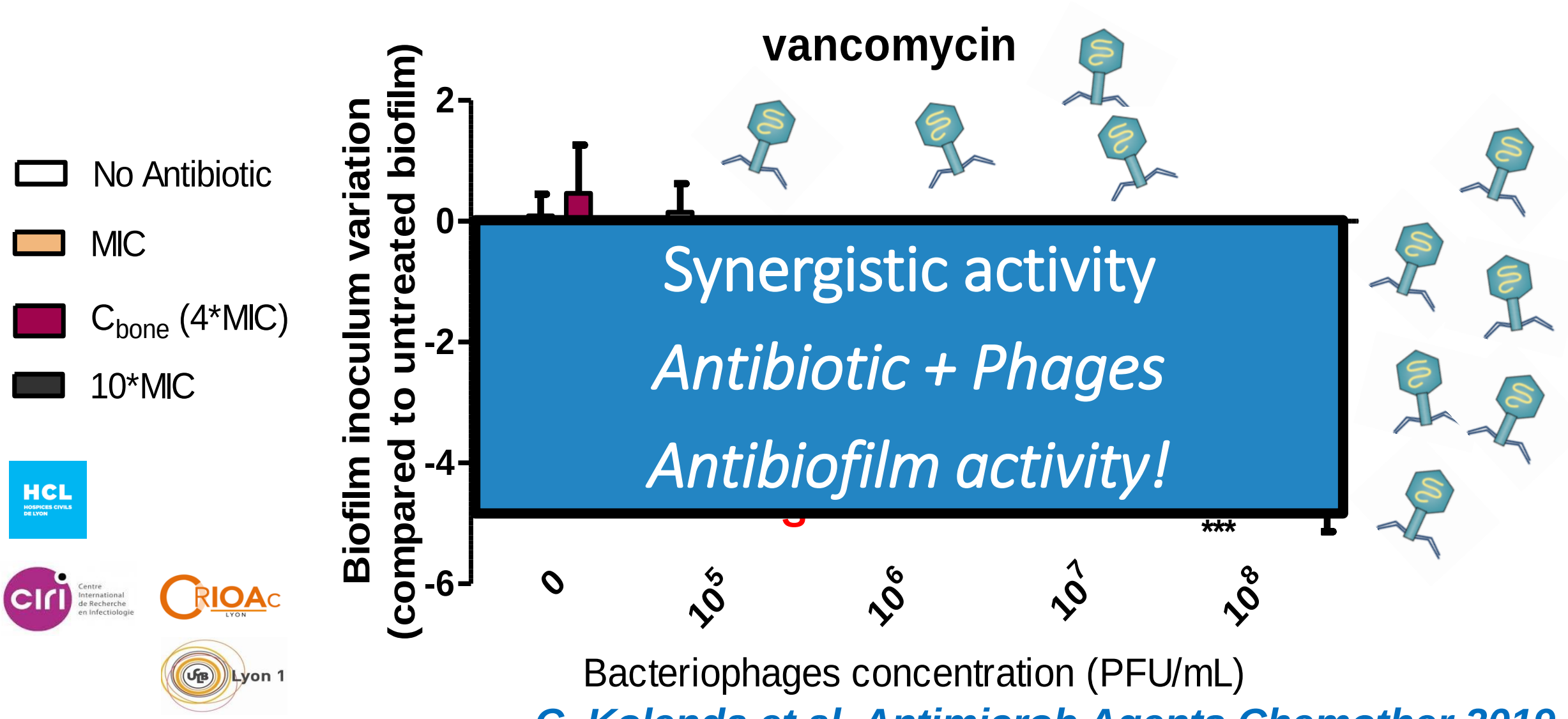
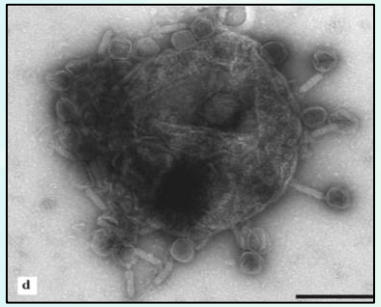


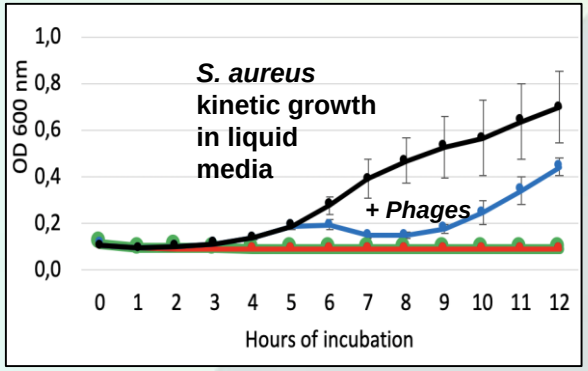
C. Kolenda et al. Antimicrob Agents Chemother 2019

Only purified lytic phages have to be used



Merabishvili et al. *PloS ONE* 2009

Etc.



Ferry et al. *OFID* 2018

?

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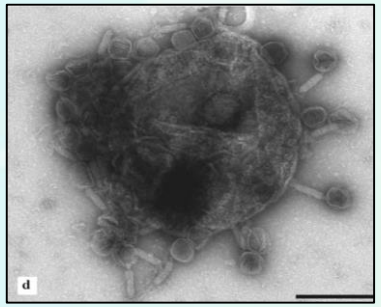

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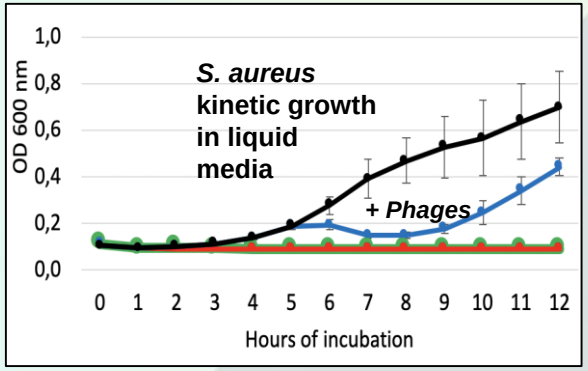
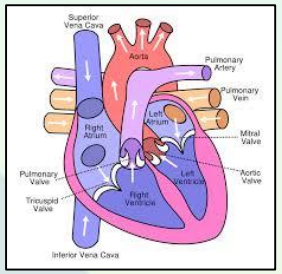


Ferry et al. *OFID* 2018

?

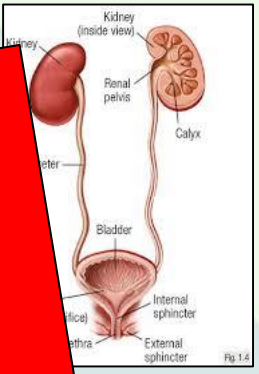
Curing bacterial disease



Prognosis factors
Host
Comorbi[illegible]

What are the relevant indications for phage therapy?

[illegible] the efficacy in each indication
Costly (≳ 1M€)
Take time (years)



Bone and joint infections

Post-trauma long-bone osteomyelitis

Surgery
(debridement & reconstruction)
Antibiotics

Chronic prosthetic-joint infection

Surgery
(prosthesis explantation)
Antibiotics

Spinal infection with abscess and bone destruction

Surgery
(debridement & stabilization)
Antibiotics

Clinical case #1

54-year-old man
Trauma with open fracture

Post-trauma tibial *S. aureus* **osteomyelitis**

Surgical debridement

Antibiotics

Failure

Management in Georgia for receiving **phage therapy** bacteriophages 10 years ago

Failure

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Failure

Clinical case #1

54-yea
Traum

Post-t
osteo

Surgic
Antibi
Failure
Manag
receiv
bacter
Failure

Sclerotic bone with biofilm requiring surgery

Skin and soft tissue damage requiring surgical coverage

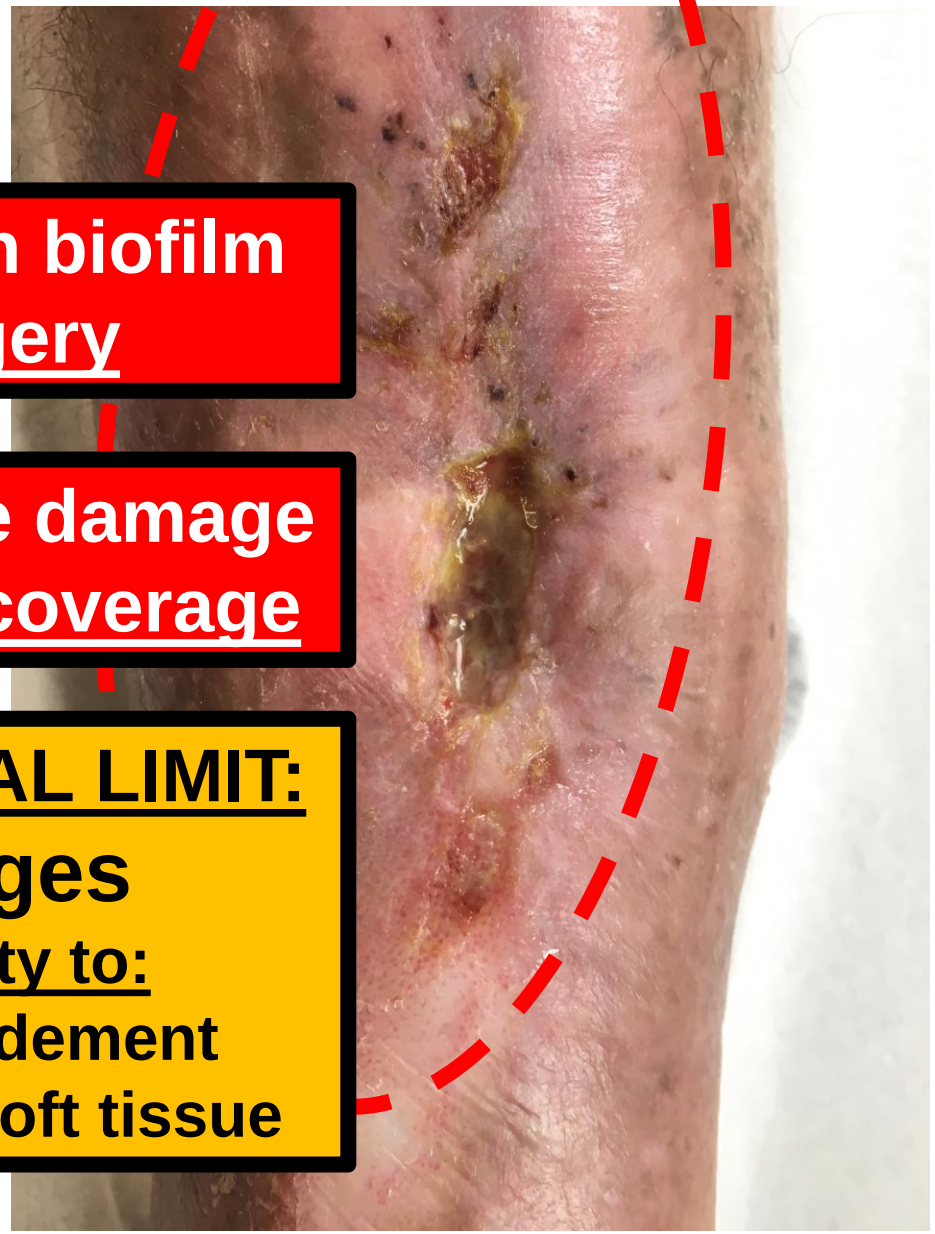
MAJOR BIOLOGICAL LIMIT:

Bacteriophages

have not the ability to:

perform bone debridement

regenerate skin and soft tissue



Docteur André RAIGA

Ancien Interne lauréat des Hôpitaux
Ex-Chef de Clinique chirurgicale à la Faculté

. . .

At the stage of bone necrosis, ***it will only succeed in stopping the progression of the infection****, but* ***it will be able to do nothing against the dead bone deprived of circulation; this bone will become sequestered and the lesion is no longer a matter of surgery.*** *To do otherwise is to commit, in my opinion, an error of therapeutic indication.*

Au stade de nécrose osseuse, il ne réussira plus qu'à cnrayer la progression de l'infection, mais il ne pourra plus rien contre l'os que la mort a privé de circulation ; cet os va se séquestrer et la lésion ne relève plus maintenant que de la chirurgie. Agir autrement c'est commettre, à mon sens, une erreur d'indication thérapeutique.

1961

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Surgery
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Antibiotics

Chronic prosthetic-joint infection

Surgery
(prosthesis explantation)
Antibiotics

Spinal infection with abscess and bone destruction

Surgery
(debridement & stabilization)
Antibiotics

Clinical case #2

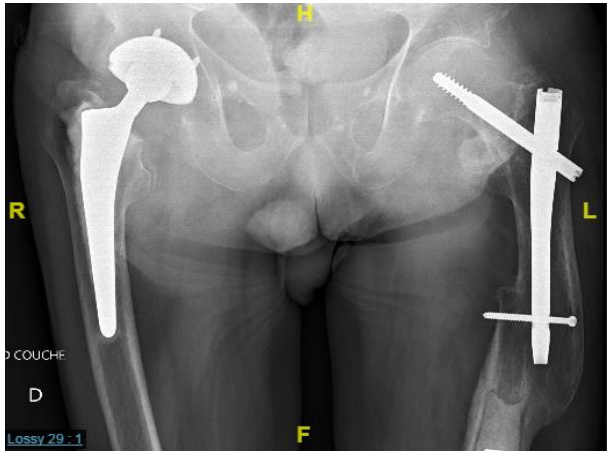
80-year-old man

<u>Relapsing *S. aureus*</u> prosthetic left knee infection (past revision)

<u>Failure</u>

Complex orthopaedic situation with past femoral fracture

Impossible to walk (painful knee)

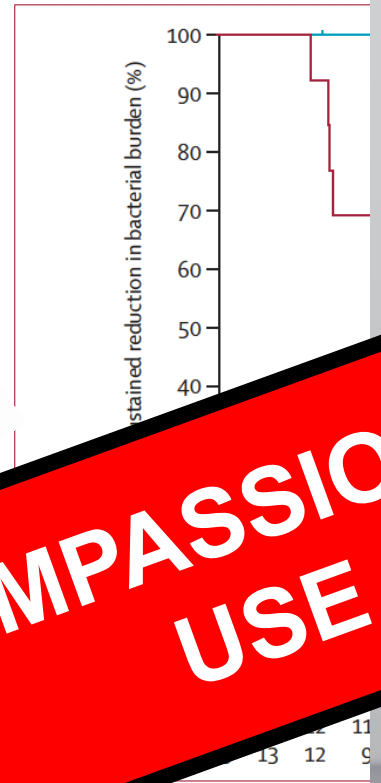



Septic arthritis


Fistula and purulent discharge

Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial

Patrick Jault, Thomas Leclerc, Serge J
Ronan Le Floch, Jean Vivien Schaal, C



2: Time to observe reduction
Kaplan-Meier analysis of median time
highest daily bacterial burden compared with day 0. HR=hazard ratio. PP1131=cocktail of 12 natural lytic anti-*Pseudomonas aeruginosa* bacteriophages.

COMPASSIONATE USE

osa

CYDES

Lancet Infect Dis 2018

PHOSA

PHERECYDES PHARMA

PHOSA & Phagothérapie | Consortium PHOSA | Communication | Contact

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE

LES PÔLES DE COMPÉTITIVITÉ
MOTEURS DE CROISSANCE ET D'EMPLOI

ARF ASSOCIATION DES RÉGIONS DE FRANCE

bpifrance

CRIOAc LYON

BioFilm Control

UCBL Lyon 1

Vivexia laboratory

HCL HOSPICES CIVILS DE LYON

ciri Centre International de Recherche en Infectiologie

CENTRE HOSPITALIER INTERCOMMUNAL
VILLENEUVE-SAINT-GEORGES
Lucie & Raymond AUBRAC

<u>Phage discovery</u>
to find active bacteriophages against Staphylococci

Phages anti-S. aureus

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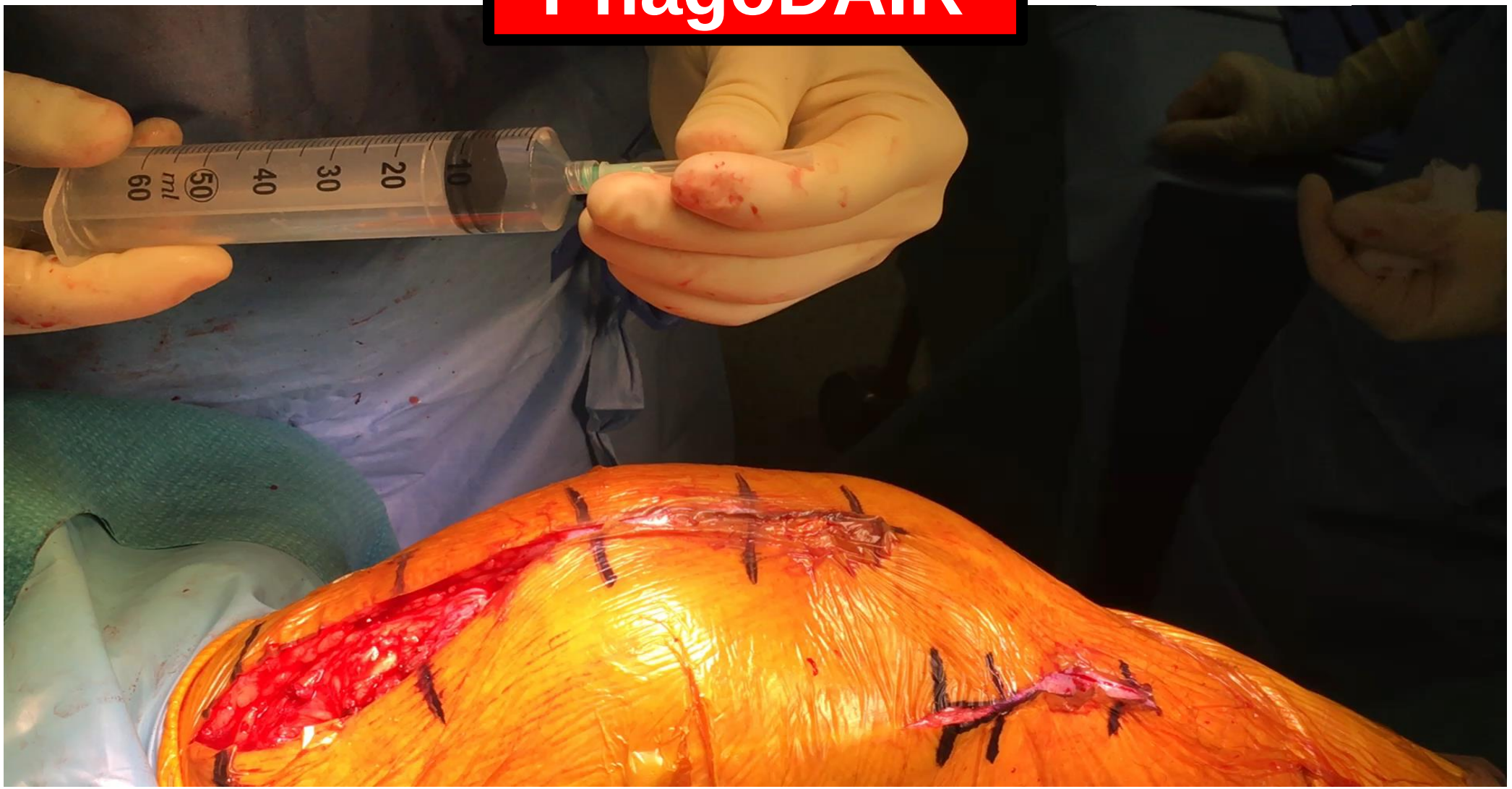
“Debridement And Implant Retention” (DAIR)

Ferry T. et al. 2020

“PhagoDAIR”

frontiers in Medicine



<u>One shot</u> peroperative phage application after “DAIR”

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CRIOAc LYON

Clinical case #2

<u>Post-operative</u> antibiotics:

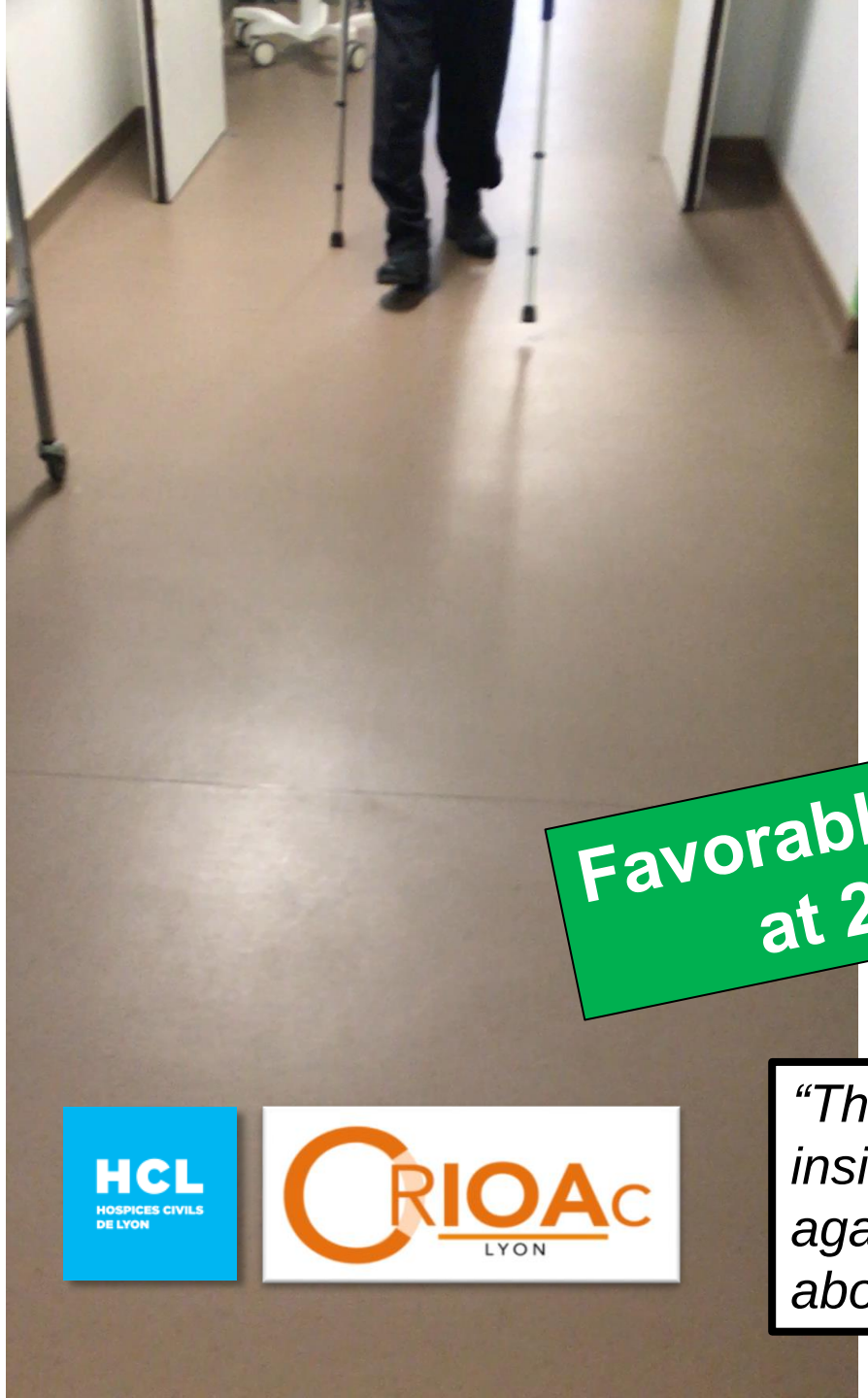
Daptomycin + Rifampin

<u>At day 4 </u>(only MSSA in all intraoperative samples):

Levofloxacin + Rifampin

<u>Then:</u>

Cefalexin as suppressive antimicrobial therapy



Favorable outcome at 2 years

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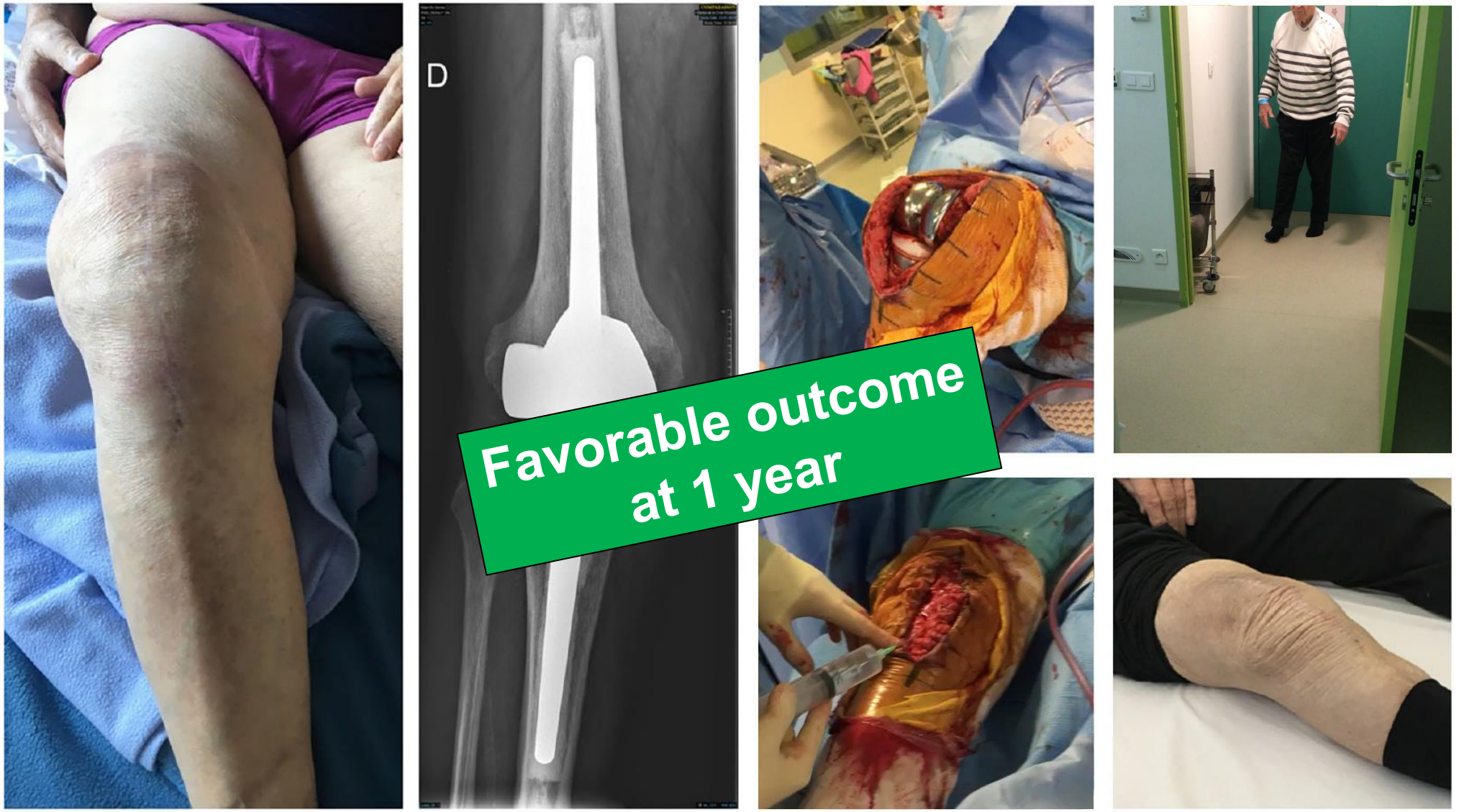
“The bacteriophages saved my life, he insists. I never thought one day to walk again. And to say that doctors were talking about cutting my leg off!” R.N.

frontiers in Medicine

T. Ferry et al.

CASE REPORT
published: 16 November 2020
doi: 10.3389/fmed.2020.570572



Lyon 1

CRIOAc LYON

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frontiers in Medicine

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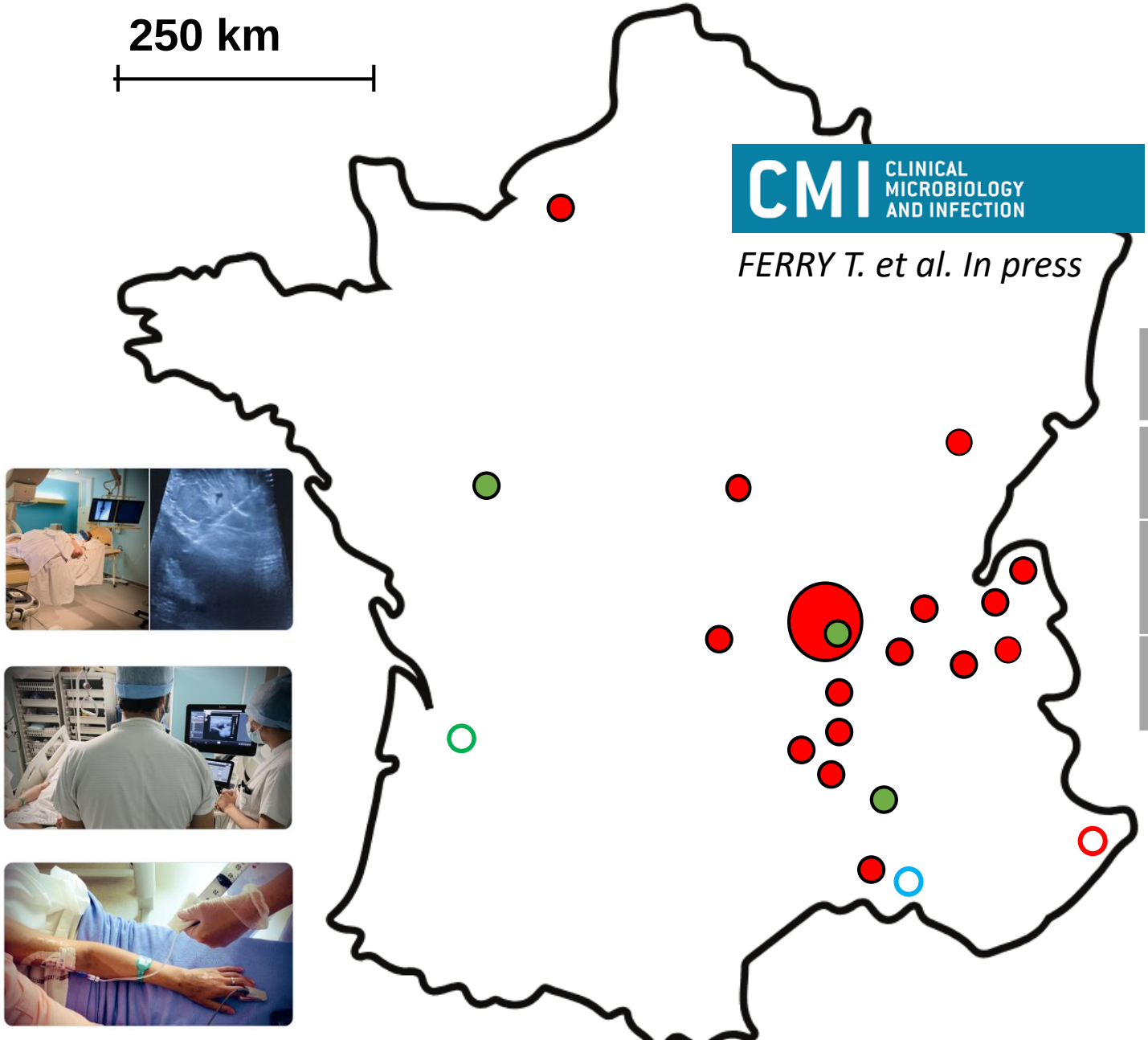
Implementation of a Phage Therapy Center in a CRIOAc



CMI CLINICAL MICROBIOLOGY AND INFECTION

FERRY T. et al. In press

HCL HOSPICES CIVILS DE LYON

PHAGE*in*LYON

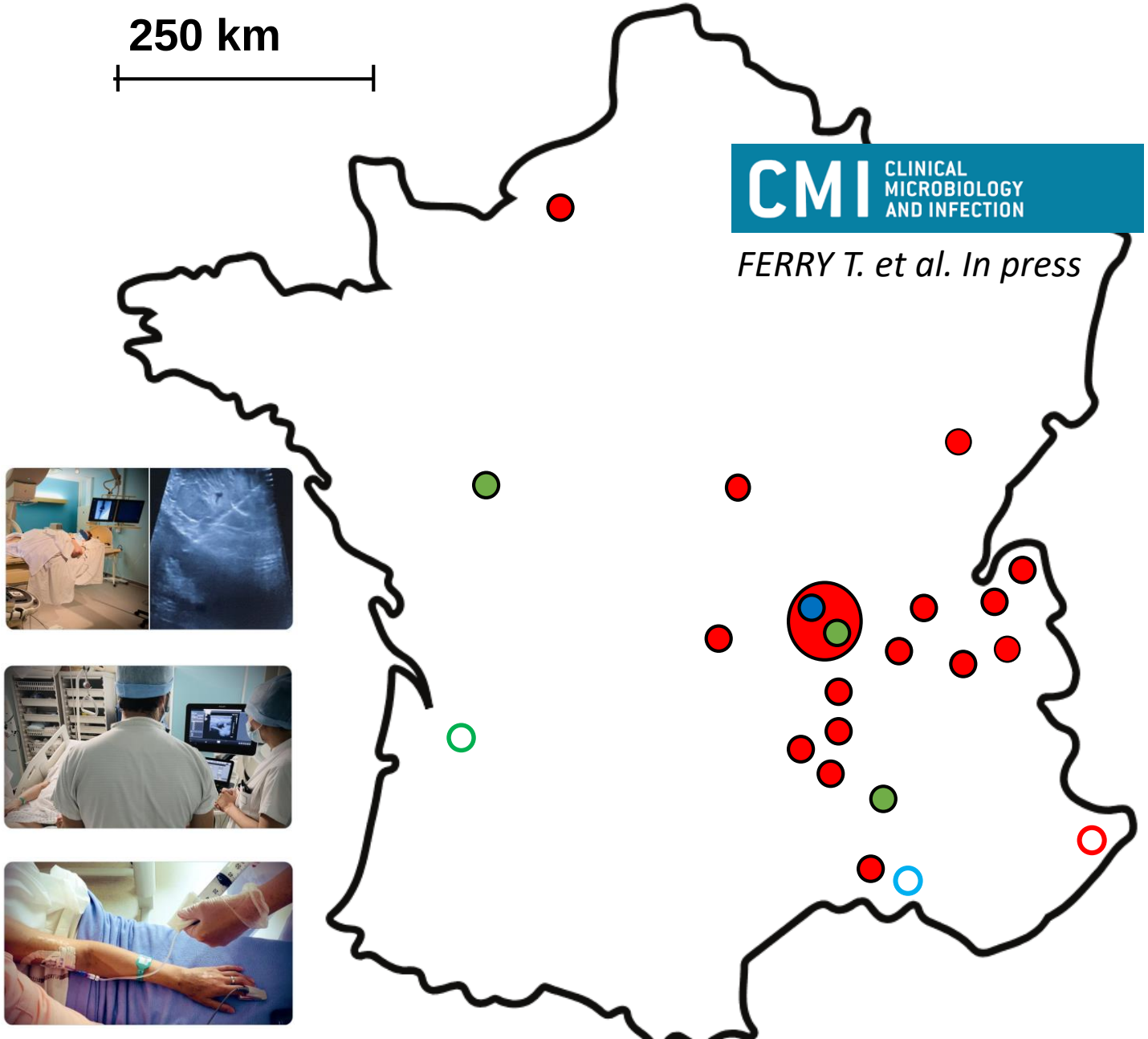
FONDATION HCL HOSPICES CIVILS DE LYON

Lyon 1 · CRIOAc LYON · ciri Centre International de Recherche en Infectiologie

Number of patients	2017	2018	2019	2020	Total
Managed in CRIOAc Lyon	557	594	647	520	**2318**
For whom a phagogram was performed	7 (1.2%)	10 (1.7%)	17 (2.6%)	23 (4.4%)	**57 (2.4%)**
For whom phage therapy was done	4 (0.7%)	2 (0.3%)	8 (1.2%)	7 (1.3%)	**21 (0.9%)**

●○ BJI ●○ Endocarditis ●○ Pneumonia

Implementation of a Phage Therapy Center in a CRIOAc



CMI CLINICAL MICROBIOLOGY AND INFECTION

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HCL HOSPICES CIVILS DE LYON — PHAGE*in*LYON — FONDATION HCL HOSPICES CIVILS DE LYON

Lyon 1 — CRIOAc LYON — ciri Centre International de Recherche en Infectiologie

30 patients in Lyon since 2017

- 27 with phages from PHERECYDES PHARMA
- 3 with phages from MHKA HMRA

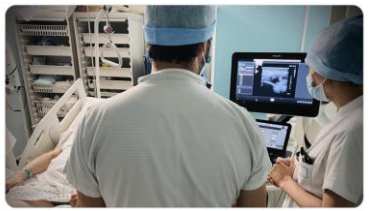
- 26 **BJI** (including **22 PJI**)
- 3 **endocarditis**
- 1 **PAVM bactériémique**

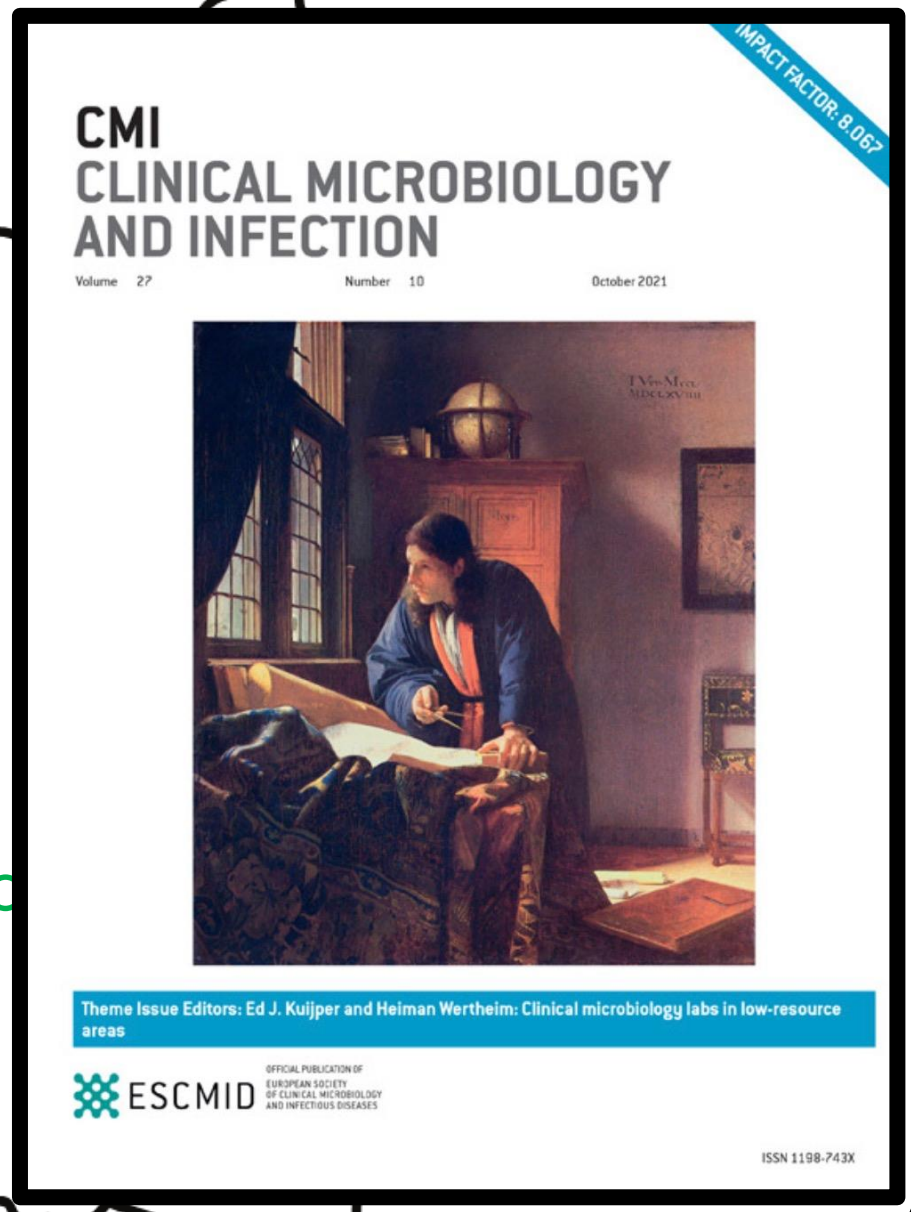
+ 3 patients managed outside Lyon

BJI **Endocarditis** **Pneumonia**

Implementation of a Phage Therapy Center in a CRIOAc

250 km





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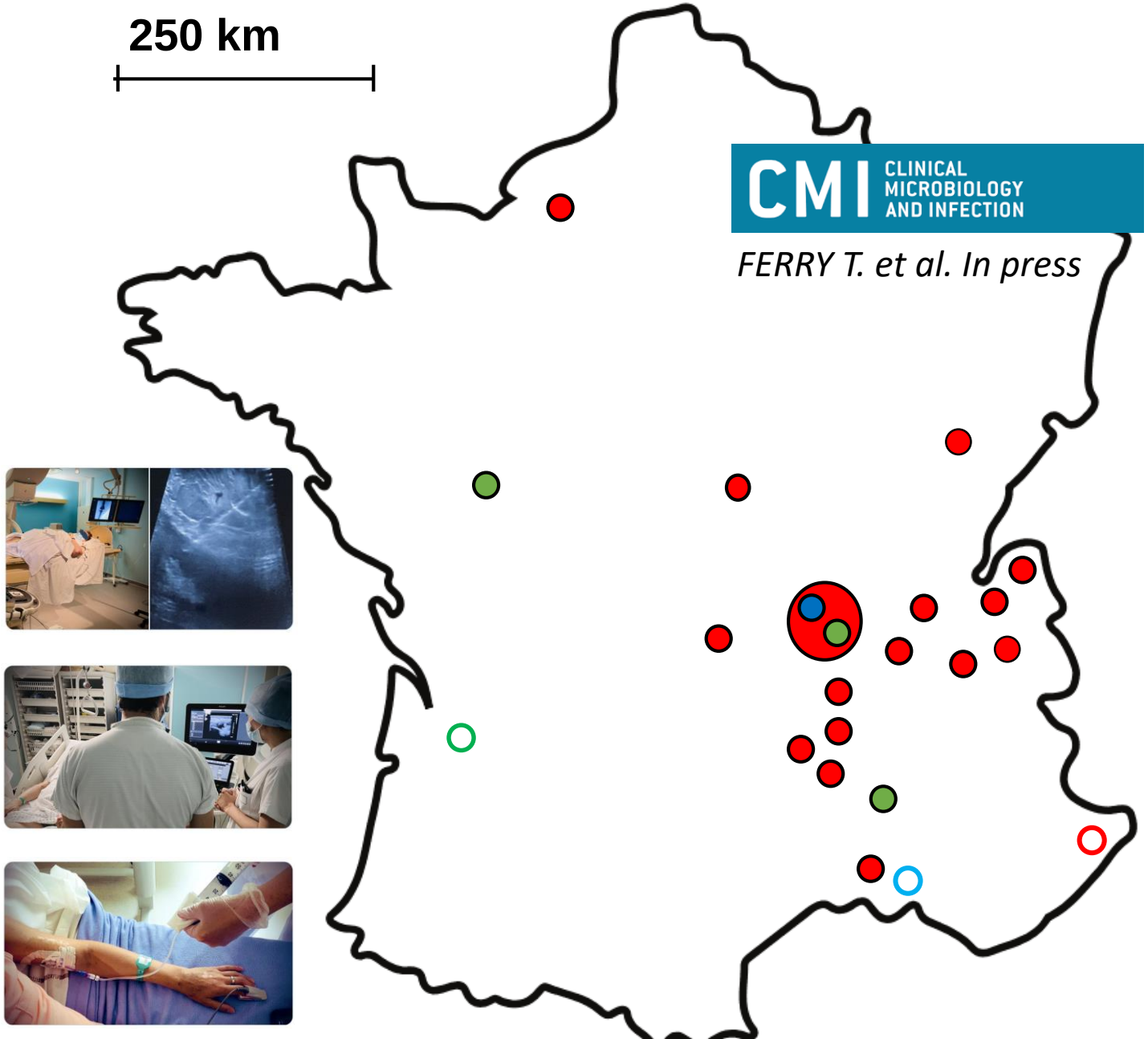

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HCL HOSPICES CIVILS DE LYON — PHAGE*in*LYON — FONDATION HCL HOSPICES CIVILS DE LYON

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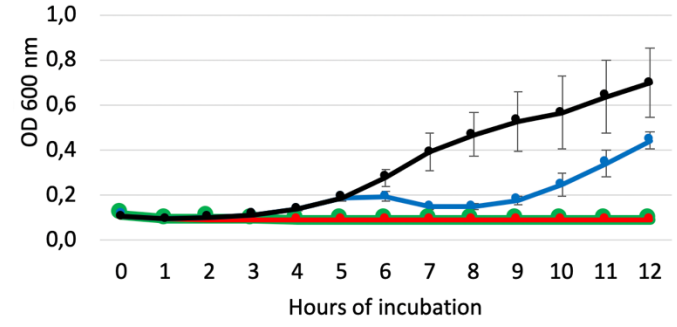
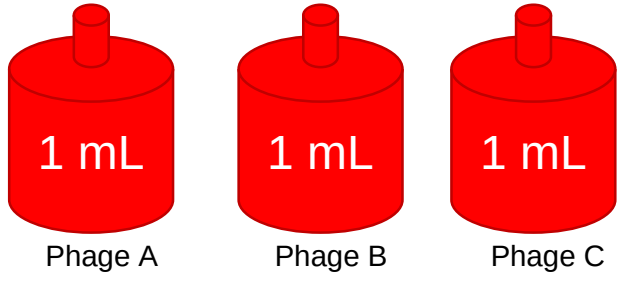
PHAGE*in*LYON team



Phagogram
Selection of active bacteriophages

Active GMP

***S. aureus* Bactériophages**



ID Clinic

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CRIOAC LYON

ADJUVANT INNOVATIVE ANTI-INFECTIVE AGENTS
OPTIMAL SEPTIC SURGERY
TARGETED AND OPTIMAL ANTIMICROBIAL THERAPY
MULTIDISCIPLINAR MEETING

Surgery

HCL HOSPICES CIVILS DE LYON

Lab

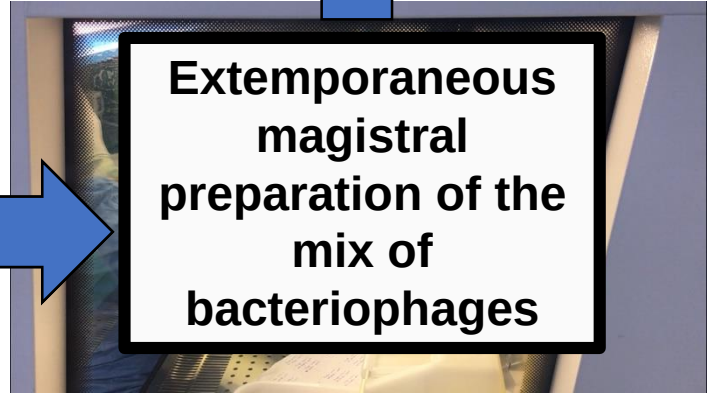
HCL HOSPICES CIVILS DE LYON

Under the supervision of

ansm
Agence nationale de sécurité du médicament et des produits de santé
French Health Authority

Pharmacy

HCL HOSPICES CIVILS DE LYON



Extemporaneous magistral preparation of the mix of bacteriophages

Bone and joint infections

Post-trauma long-bone osteomyelitis

Surgery
(debridement & reconstructio
Antibiotics

Chronic prosthetic-joint infection

Clinical trial
PhagoDAIR
Janvier 2022

Spinal infection with abscess and bone destruction

Surgery
lebridement & stabilization)
Antibiotics

Clinical case #3

74-year-old man

Melanoma treated with anti-PD1

Catheter-related ***P. aeruginosa*** **bacteriemia** in January 2018

Spinal pain summer 2018

Spondylodiscitis with **spinal abscess**

Pandrug-resistant *P. aeruginosa* in culture!

Clinical case #3

74-year-old man

Melanoma treated with anti-PD1

Catheter-related ***P. aeruginosa*** **bacteriemia** in January 2018

Spinal pain summer 2018

Spondylodiscitis with **spinal abscess**

Pandrug-resistant *P. aeruginosa* in culture!

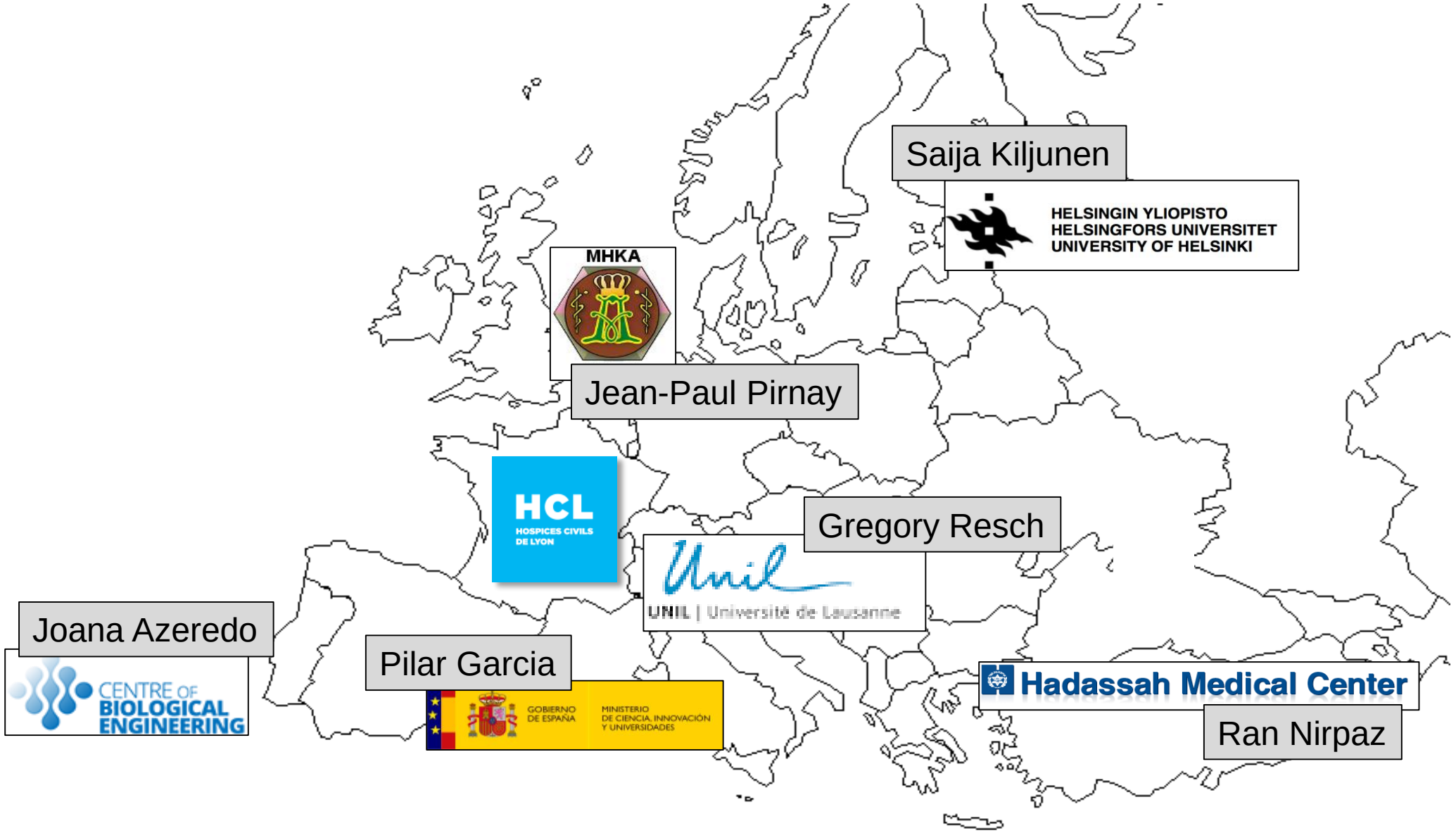
	Pseudomonas aeruginosa CMI (mg/l)
Ticarcilline + Ac. Clav	R (> 64)
Pipéracilline	R (> 64)
Pipéracilline + Tazobactam	R (> 64)
Ceftazidime	R (> 32)
Céfépime	R (> 32)
Aztréonam	R (> 32)
Imipénème	R (> 8)
Meropeneme	R (> 8)
Gentamicine	R (> 8)
Tobramycine	R (> 8)
Amikacine	R (> 32)
Ciprofloxacine	R (> 2)
Lévofloxacine	R (> 4)
Cotrimoxazole	R
Colistine	S (8) ⇨ R
Colistine (Etest)	S E-test : 1 ⇨ R
Ceftolozane-tazobactam (Etest)	R E-test : > 256
Ceftazidime-Avibactam (Etest)	R E-test : 64

PHERECYDES PHARMA

AMPLIPHI BIOSCIENCES CORPORATION

The strain was also spontaneously resistant to bacteriophages !!!

Potential European academic collaborations



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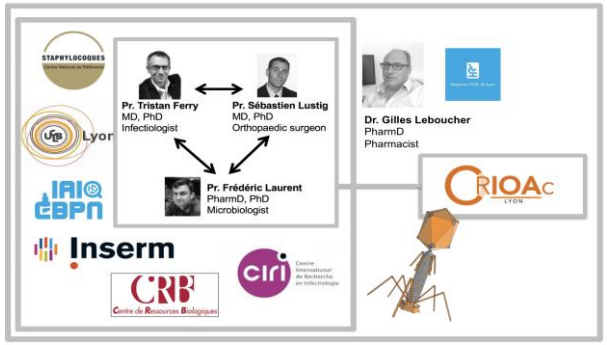
French Health Authority

Potential European academic collaborations

Lyon Phage team



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Potential European academic collaborations

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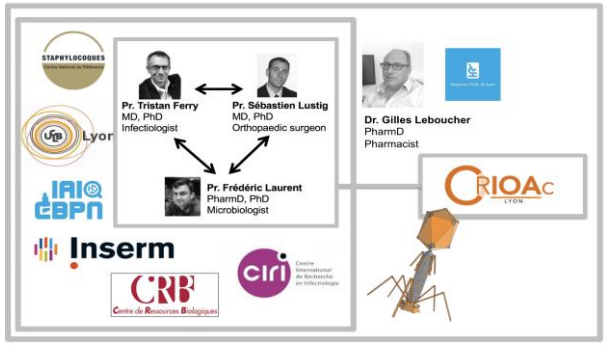
French Health Authority

MHKA

Jean-Paul Pirnay

Gregory Resch

Lyon Phage team



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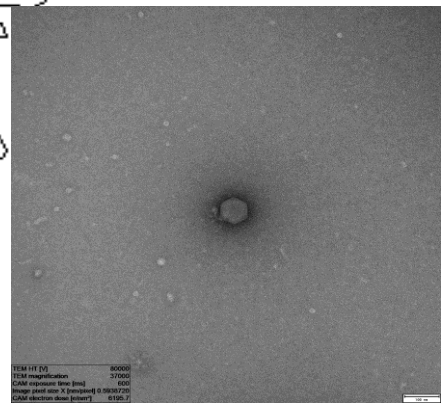

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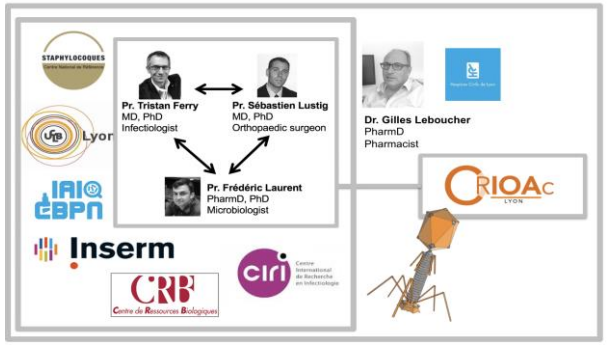

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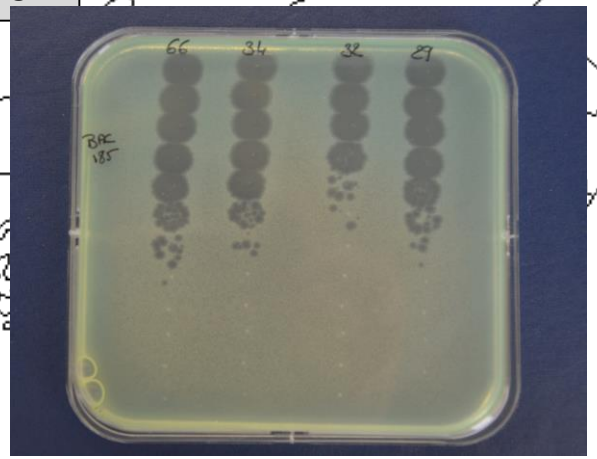
Gregory Resch

Unil
UNIL | Université de [illegible]anne



Potential European academic collaborations

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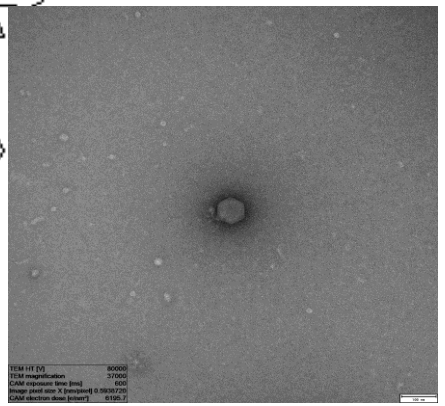

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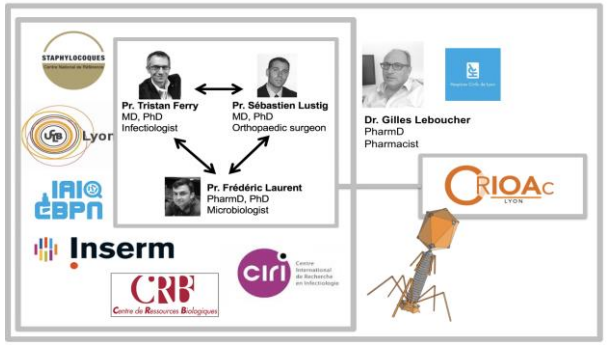

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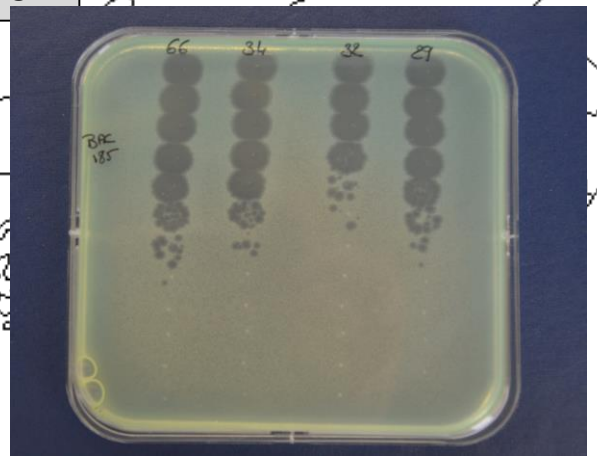

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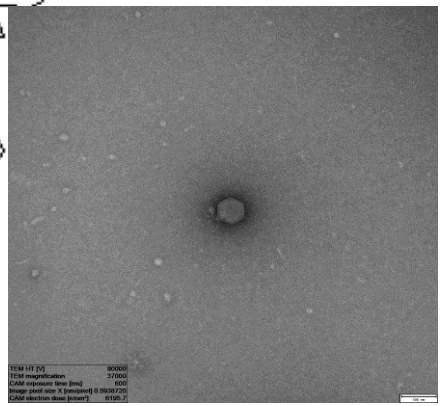
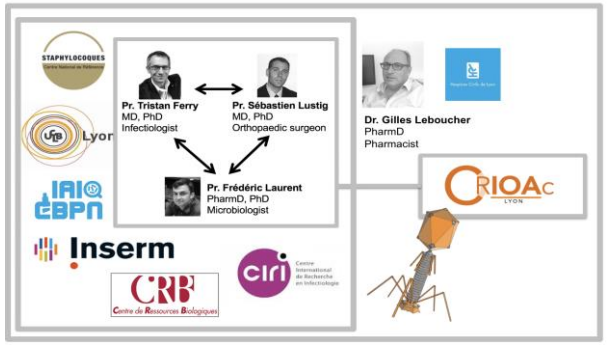


Lyon Phage tea

Jean-Paul Pirnay

Gregory Resch



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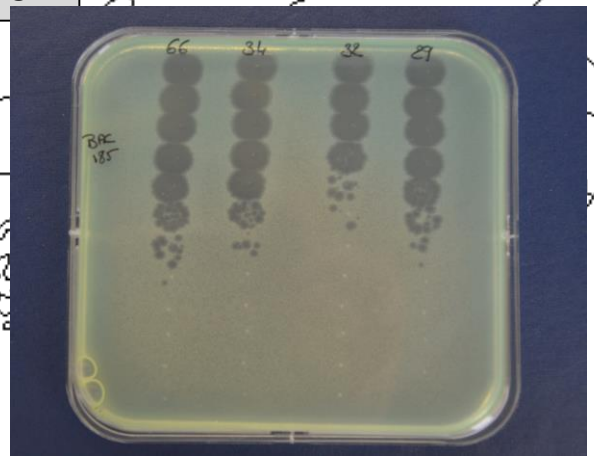

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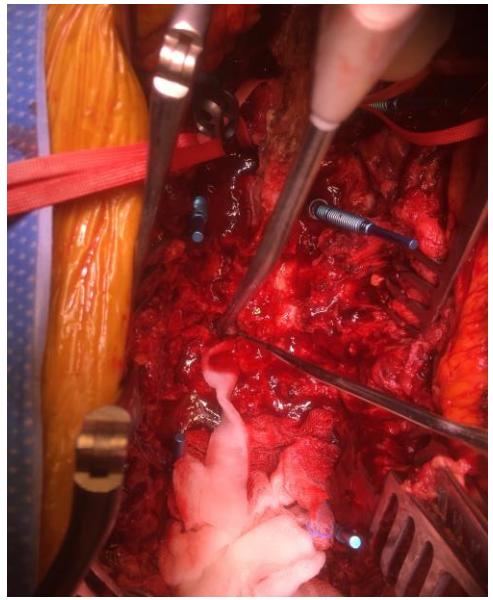
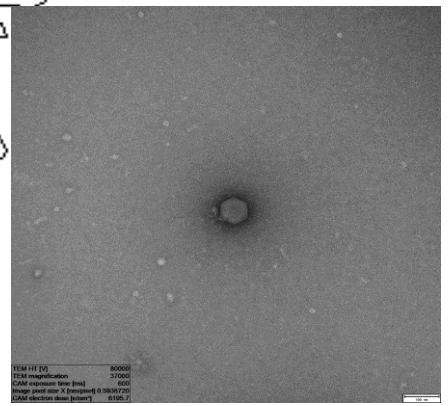
French Health Authority

Potential European academic collaborations





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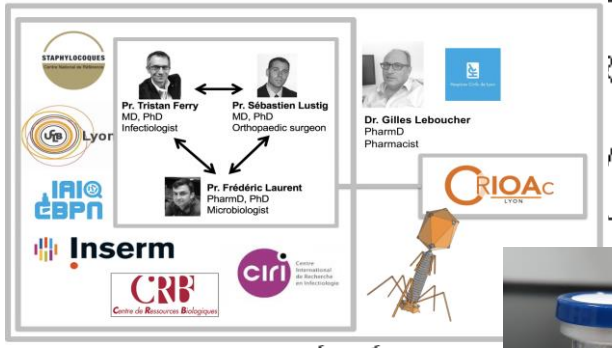

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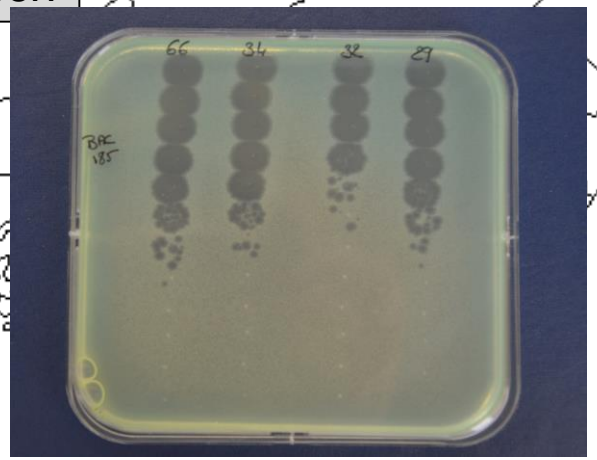
Céfiderocol
ATU



Personalized production and administration of bacteriophages: lessons learned from a unique European academic collaboration to treat a patient with pandrug-resistant spinal *P. aeruginosa* infection

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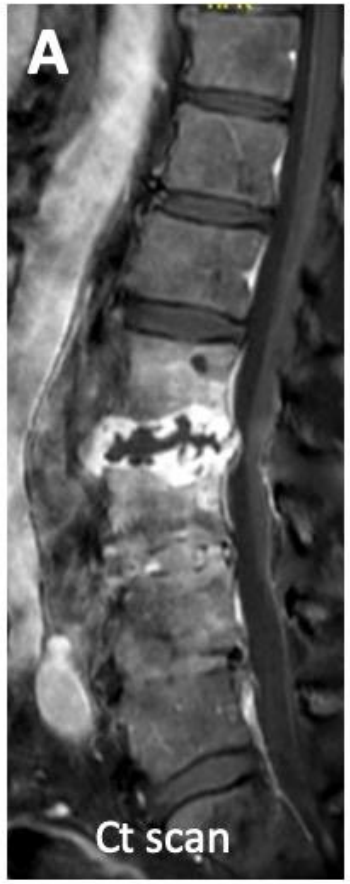

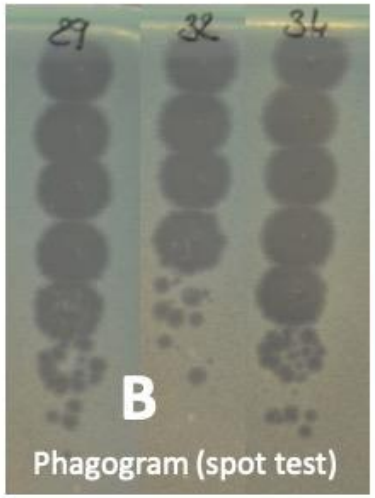

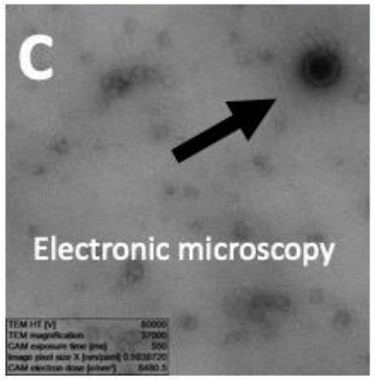

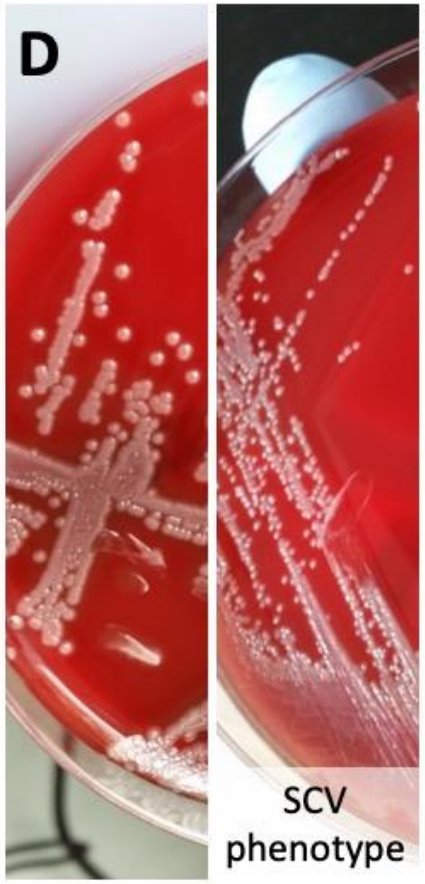

30th ECCMID

Paris, France
18 –21 April 2020

CRIOAc LYON

Conclusions: Personalized phage therapy is a potential adjunct treatment for patients with complex BJI due to pandrug-resistant bacteria. **In addition to industrial phages under development, academic collaborative research is crucial to develop personalized phage therapy.**

Personalized production and administration of bacteriophages: lessons learned from a unique European academic collaboration to treat a patient with pandrug-resistant spinal *P. aeruginosa* infection

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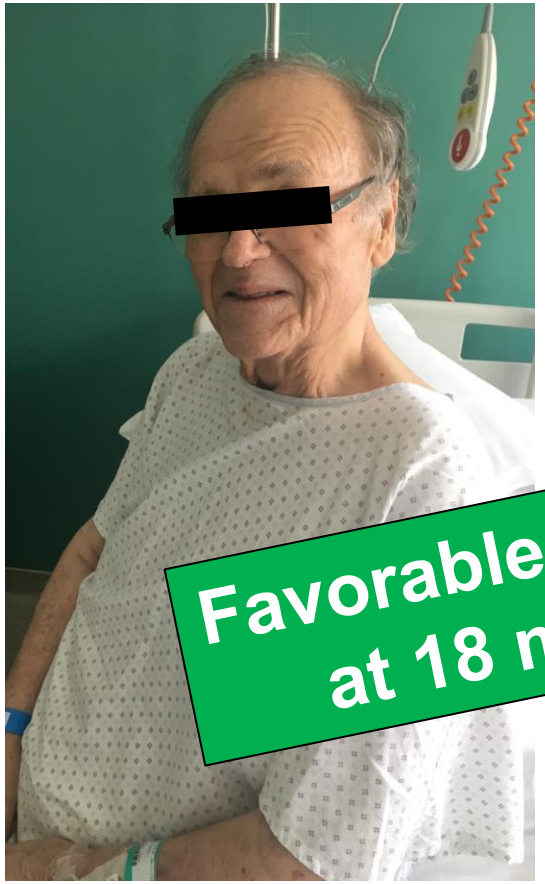

Favorable outcome at 18 months

30th ECCMID

Paris, France
18 –21 April 2020

CRIOAc LYON

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Bone and joint infections

Post-trauma long-bone osteomyelitis

Surgery
(debridement & reconstruction)
Antibiotics

Chronic prosthetic-joint infection

Surgery
(prosthesis explantation)
Antibiotics

Spinal infection with abscess and bone destruction

Surgery
(debridement & stabilization)
Antibiotics

‘Debridement And Implant Retention’ (DAIR) with local administration of personalized cocktail of bacteriophages (PhagoDAIR) followed by suppressive antibiotherapy as salvage therapy in patients with relapsing prosthetic knee infection

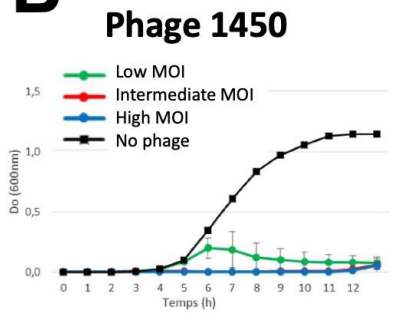
Phago DAIR

CRIOAc LYON

A

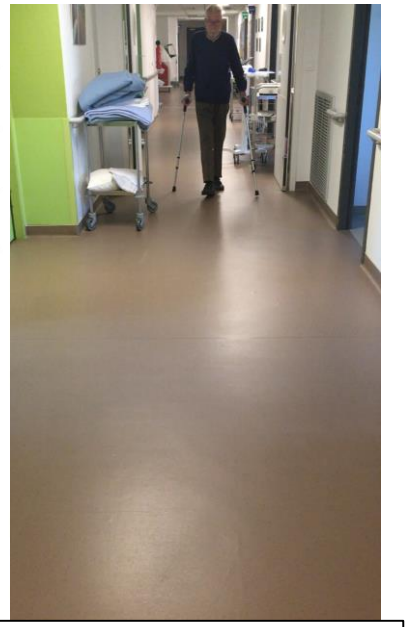
Left PKI with purulent joint effusion

B



Phagogram (Killing assay)

D



Favorable outcome at 1 year

30th ECCMID

Paris, France
18 –21 April 2020

PHERECYDES PHARMA

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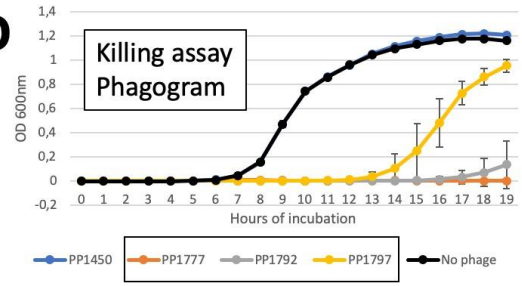
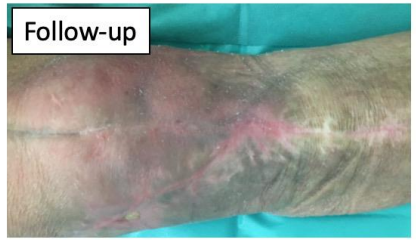
Conclusions: **Personalized bacteriophage therapy has the potential** to be used as salvage therapy during DAIR in patients with relapsing *S. aureus* and *P. aeruginosa* prosthetic knee infection, **to improve the efficacy of suppressive antibiotics, and to avoid considerable loss of function.**

Ultrasound guided local administration of personalized cocktail of bacteriophages followed by suppressive antibiotherapy as salvage therapy in patients with relapsing total femur prosthesis infection



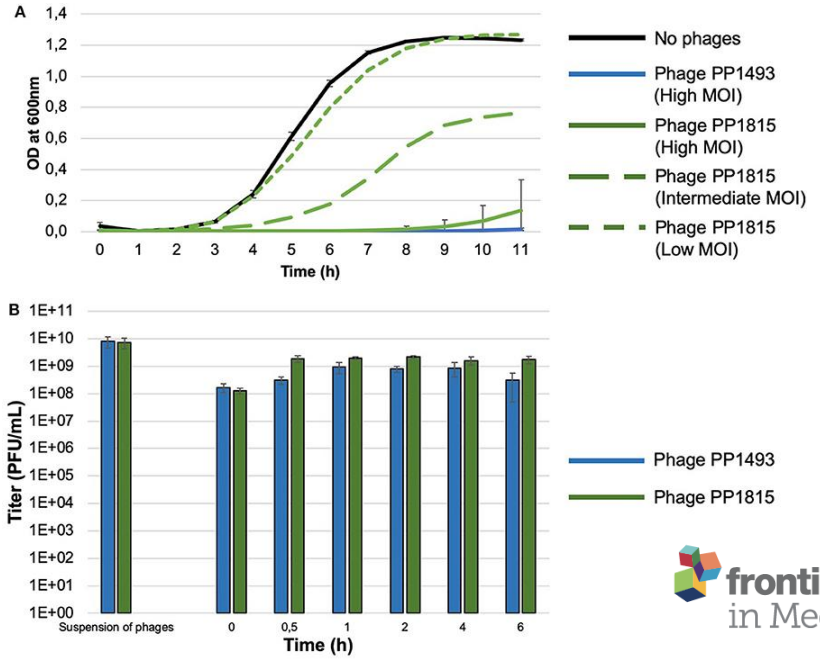


30th ECCMID
Paris, France
18 –21 April 2020

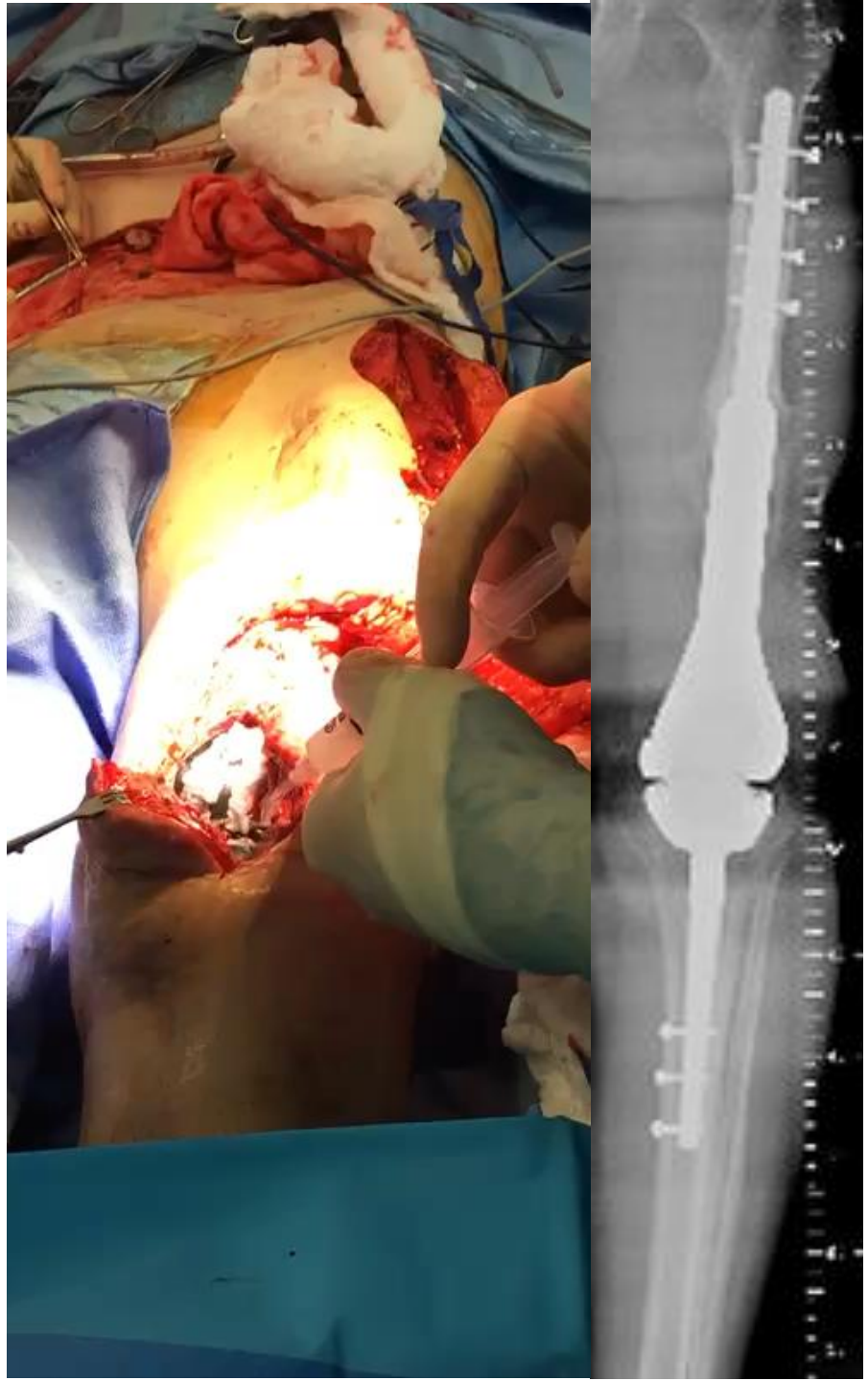
Conclusions: **Ultrasound-guided local administration** of personalized cocktail of GMP bacteriophages followed by suppressive antibiotherapy in patients with relapsing total femur PJI **has the potential to be used as salvage therapy** to control the infection and avoid disarticulation. Dramatic superinfection could be diagnosed at the time of phage administration.

The Potential Innovative Use of Bacteriophages Within the DAC® Hydrogel to Treat Patients With Knee Megaprosthesis Infection Requiring "Debridement Antibiotics and Implant Retention" and Soft Tissue Coverage as Salvage Therapy

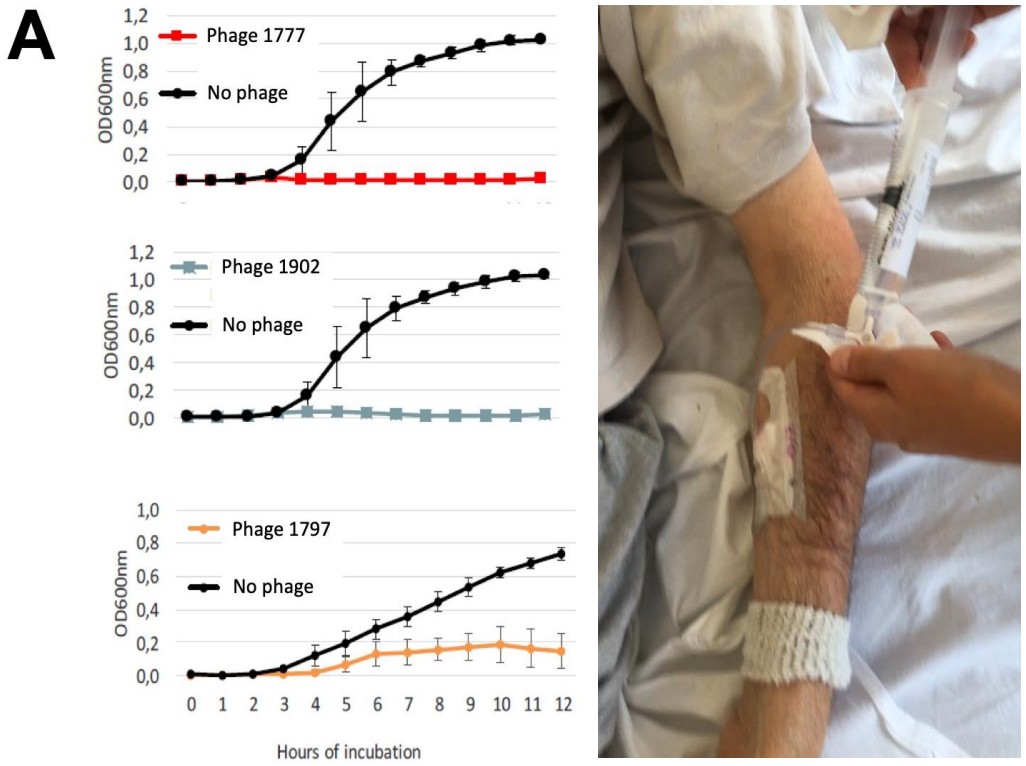
Tristan Ferry[1,2,3,4], Cécile Batailler[2,3,5], Charlotte Petitjean[6], Joseph Chateau[7], Cindy Fevre[6], Emmanuel Forestier[8], Sophie Brosset[7], Gilles Leboucher[9], Camille Kolenda[2,3,4,10], Frédéric Laurent[2,3,4,10] and Sébastien Lustig[2,3,5] on behalf of the Lyon BJI Study Group*

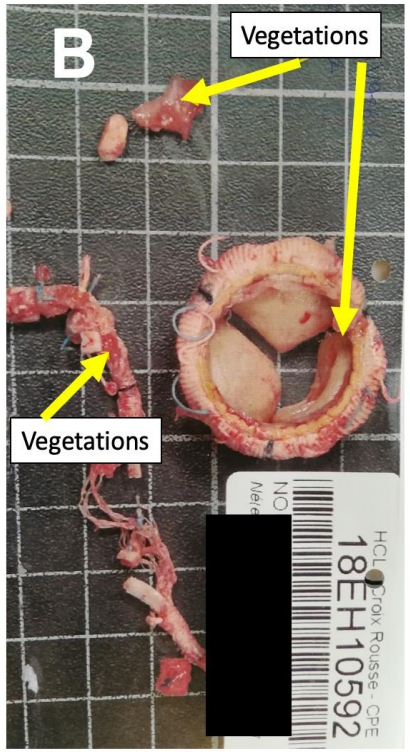


frontiers in Medicine



<u>Intravenous</u> administration of personalized cocktail of bacteriophages as salvage therapy in combination with ceftazidime/avibactam in patients with relapsing *P. aeruginosa* bacteremia: Lesson learned from two cases





30th ECCMID
Paris, France
18 –21 April 2020

PHERECYDES PHARMA

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Conclusions: **The type of filter used for the magistral preparation and the duration of the perfusion influenced the phage titer, as the titer in the patient's blood.** Personalized GMP bacteriophage therapy has the potential to be used as salvage therapy of *P. aeruginosa* intravascular implant infections.

Open Forum Infectious Diseases

BRIEF REPORT

Salvage De
Implant Re
Local Injec
of Bacterio
an Elderly
Staphyloco
Infection?

Ferry T.

The Potential Innovative Use of Bacteriophages Within the DAC® Hydrogel to Treat Patients With Knee fection Requiring biotics and and Soft Tissue ge Therapy

frontiers in Medicine

te Petitjean[6], Joseph Chateau[7], rosset[7], Gilles Leboucher[9], and Study Group

2020

Case Report: Arthroscopic "Debridement Antibiotics and Implant Retention" With Local Injection of Personalized Phage Therapy to Salvage a Relapsing *Pseudomonas Aeruginosa* Prosthetic Knee Infection

frontiers in Medicine

2021

Tristan Ferry[1,2,3,4], Camille Kolenda[2,3,4,5], Cécile Batailler[2,3,6], Romain Gaillard[3,6], Claude-Alexandre Gustave[2,3,4,5], Sébastien Lustig[2,3,6], Cindy Fevre[7], Charlotte Petitjean[7], Gilles Leboucher[8], Frédéric Laurent[2,3,4,5] and the Lyon BJI Study group*

ction

one and joint including local

application of a selected cocktail of bacteriophages

Tristan Ferry ✉, Fabien Boucher, Cindy Fevre, Thomas Perpoint, Joseph Chateau, Charlotte Petitjean, Jérôme Josse, Christian Chidiac, Guillaume L'hostis, Gilles Leboucher, ... Show more

Journal of Antimicrobial Chemotherapy, Volume 73, Issue 10, 1 October 2018, Pages 2901–2903,

doi: 10.3389/fmed.2020.570572

frontiers in Medicine

#PhagoDAIR

Where to find phages for clinical use?

- Pherecydes Pharma

- Phage community

Under the supervision of

French Health Authority

?

Where to find phages for clinical use?

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French Health Authority

?

Purified **academic** phages
Usable in the next 5 years

Where to find phages for clinical use?

- Pherecydes Pharma

- Phage community

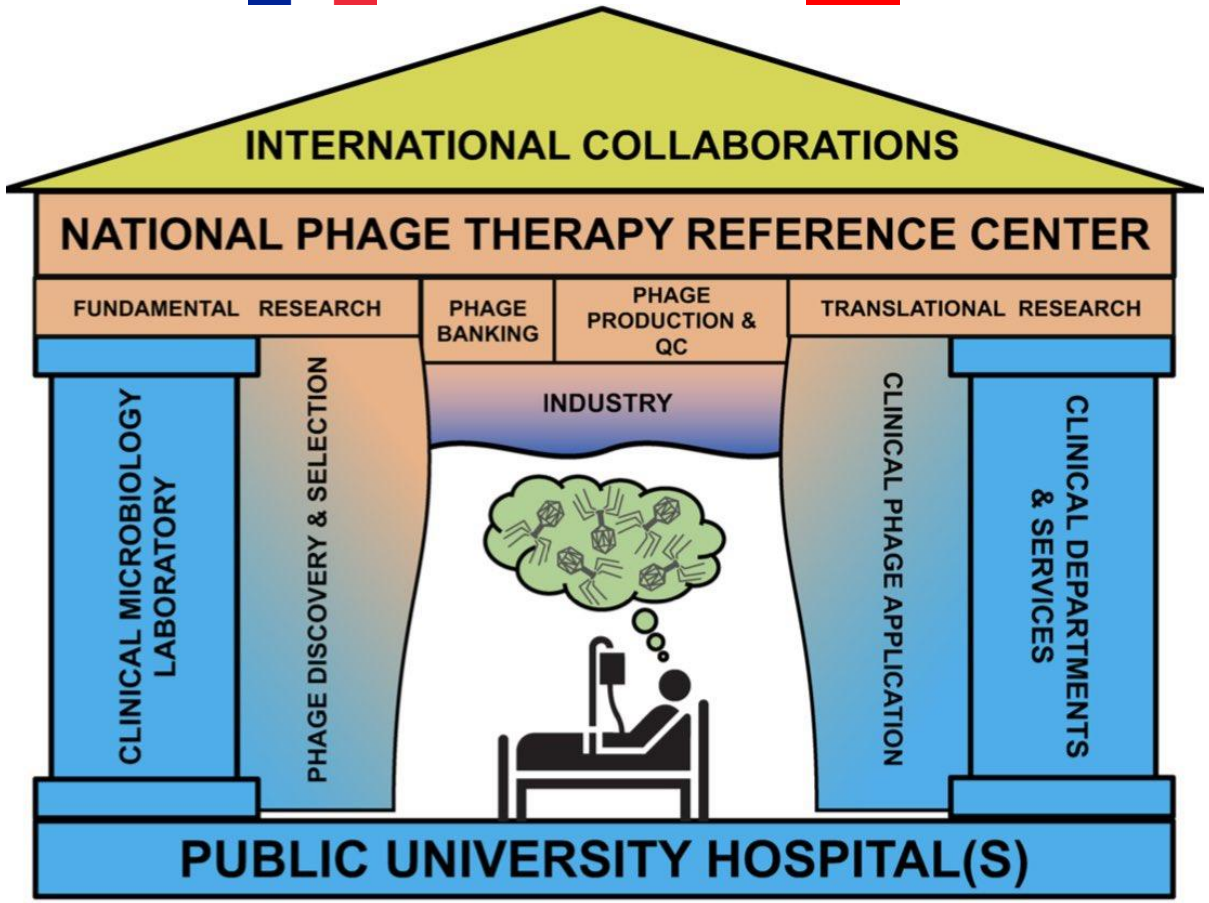
Inauguration Committee Members:

Ran Nir-Paz, **Israël**
Tristan Ferry, **France**
Patrick Soentjens, **Belgium**
Zuzanna Drulis-kawa, **Poland**
Joana Azeredo, **Portugal**

REVIEW ARTICLE

Recent progress toward the implementation of phage therapy in Western medicine

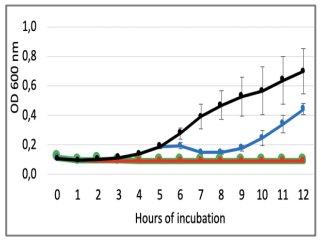
Jean-Paul Pirnay[1,†], Tristan Ferry[2,3,†] and Grégory Resch[4,*,†]



FEMS Microbiology Reviews
2021

Conclusion

- **There is a real place for phage therapy** to maximize clinical success in complex bacterial infections
- Need to identify **relevant clinical indications**
- **Expertise of referral clinical centers**
- Don’t forget **Lessons from 20th century**
- Develop and use **purified** bacteriophages
  - ▶ **30 patients treated since 2017**
- Industry / health authority / academic **collaborations**
- Need for **Phage discovery**, **banking**, **susceptibility**, to personalize the therapy
- **Need for national phage**
- Clinical trials have to be p
  potential benefit in severe



Clinical trial
PhagoDAIR
Janvier 2022

Lyon BJI Study group

Coordinator: Tristan Ferry

Infectious Diseases Specialists – Tristan Ferry, Florent Valour, Thomas Perpoint, Florence Ader, Sandrine Roux, Agathe Becker, Claire Triffault-Fillit, Anne Conrad, Cécile Pouderoux, Pierre Chauvelot, Paul Chabert, Johanna Lippman, Evelyne Braun

Surgeons – Sébastien Lustig, Elvire Servien, Cécile Batailler, Stanislas Gunst, Axel Schmidt, Elliot Sappey-Marinier, Quentin Ode, Michel-Henry Fessy, Anthony Viste, Jean-Luc Besse, Philippe Chaudier, Lucie Louboutin, Adrien Van Haecke, Marcelle Mercier, Vincent Belgaid, Aram Gazarian, Arnaud Walch, Antoine Bertani, Frédéric Rongieras, Sébastien Martres, Franck Trouillet, Cédric Barrey, Ali Mojallal, Sophie Brosset, Camille Hanriat, Hélène Person, Philippe Céruse, Carine Fuchsmann, Arnaud Gleizal;

Anesthesiologists – Frédéric Aubrun, Mikhail Dziadzko, Caroline Macabéo, Dana Patrascu;

Microbiologists – Frederic Laurent, Laetitia Beraud, Tiphaine Roussel-Gaillard, Céline Dupieux, Camille Kolenda, Jérôme Josse;

Imaging – Fabien Craighero, Loic Boussel, Jean-Baptiste Pialat, Isabelle Morelec;

PK/PD specialists – Michel Tod, Marie-Claude Gagnieu, Sylvain Goutelle;

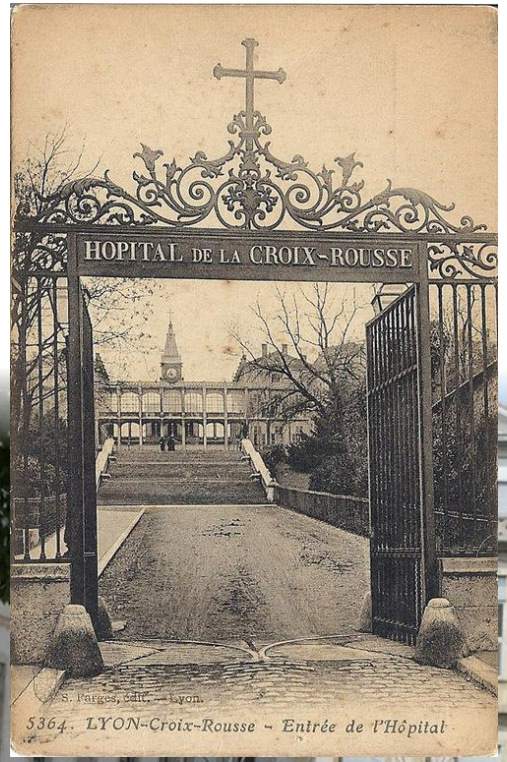
Clinical research assistant and database manager– Eugénie Mabrut

PHAGE*in*LYON

Coordinators: Tristan Ferry and Frédéric Laurent

Mathieu Medina, Camille kolenda, Floriane Laumay, Melanie Bonhomme, Leslie Blazere, Tiphaine Legendre, Eline Terrazzoni, Fabrice Pirot, Camille Merienne, Samira Filali, Benjamine Lapras, Gilles Leboucher, Thomas Briot.

Croix-Rousse Hospital



Lyon 1

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ciri Centre International de Recherche en Infectiologie

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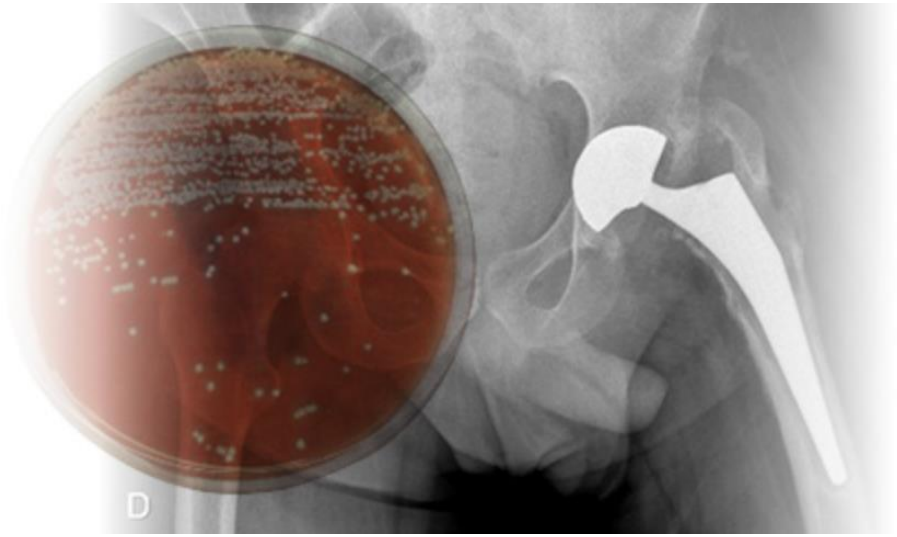
http://www.crioac-lyon.fr



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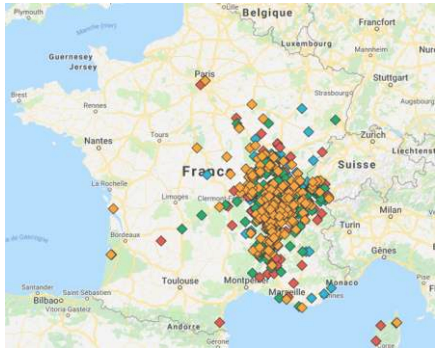

Lyon 1

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